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PREVENTION AND CONTROL OF POSTOPERATIVE WOUND INFECTIONS OWING TO *STAPHYLOCOCCUS AUREUS**

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BOSTON

ATTENTION was called in a previous paper[1] to the increasing number of antibiotic-resistant strains of *Staphylococcus aureus,* or *Micrococcus pyogenes* (var. *aureus*), being recovered from hospital patients and personnel since the introduction of penicillin. Data were presented showing that the postoperative infection rate of clean wounds had increased over a five-year period (1949-1953) at the Massachusetts Memorial Hospitals despite the use of prophylactic antibiotics. Analysis of the hospital carrier rate and the floras of infected wounds at that time suggested that the increase in sepsis was related to an abnormally high carrier rate of penicillin-resistant *Staph. aureus* as a result of the widespread and prolonged use of penicillin. It was postulated that the routine and extensive use of "prophylactic" antibiotics in surgery might therefore have an unfavorable effect upon the postoperative infection rate.

It is probable that this experience with wound infections is not an isolated one. An informed guess, based on visits to various hospitals and discussions with surgeons who have described outbreaks of wound infections, is that in some surgical units recent epidemics of postoperative sepsis owing to *Staph. aureus* have reached serious proportions, with infection rates considerably higher than reported here. But, since surgical services rarely collect or publish accurate data on wound infections, it is difficult to judge the extent to which these epidemics affect the over-all infection rate or their relation to antibiotic-resistant organisms in a particular hospital. One similar experience was documented last year by Blowers et al.[2] from a thoracic-surgery unit in England. Their wound-infection rate increased from 2 per cent in 1949 to 10.9 per cent during the first five months of 1952, when there was a high patient and personnel carrier rate of *Staph. aureus.* In 1953, after closure of the unit for reorganization, the infection rate was reduced to 3.9 per cent, and the carrier rate fell from 74 to 37 per cent. In 1954, however, their infection rate again reached 6.2 per cent.

These facts are in keeping with the general impression gained from the current medical literature and recent meetings — namely, that the number of patients with malignant forms of staphylococcal disease being admitted to hospitals has not increased but that there is reason to believe that small epidemics or outbreaks are occurring sporadically in hospital patients in certain specialized situations.

It is the purpose of this paper to describe measures taken to diminish this infection rate, to present a continuation of wound-infection statistics for 1954 and 1955 and to discuss the problem of staphylococcal wound sepsis in the light of present knowledge.

During the last two years at the Massachusetts Memorial Hospitals the carrier rate of *Staph. aureus* and the incidence of penicillin-resistant strains in carriers have been significantly reduced, and the postoperative wound-infection rate has been cut almost in half.

CORRECTIVE MEASURES

During the latter part of 1953 and early 1954 various measures to prevent crosscontamination and the dissemination of antibiotic-resistant bacteria were inaugurated. These measures were not introduced simultaneously but came into use gradually over the course of several months; nor were they on a compulsory basis. Their use was encouraged by frequent educational programs at staff meetings and by monthly presentations of the wound-infection rate. Participation on the part of the staff was generally good, but there were lapses by some individuals and partial or no participation by a few. The general surgical patients were usually on the same wards with those of other specialty surgical services not involved in the program. The following is a discussion and brief summary of the preventive program.

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Use of Antibiotics

Routine antibiotic prophylaxis on the house service was abandoned late in 1953 and by the middle of 1954 had been largely curtailed on the private service. At present it is rare to find a patient receiving antibiotics for prophylaxis before or after a "clean" operation.

Several points were stressed. In the first place the use of antibiotics was reduced to a minimum, being limited to treatment of established infections — not for the mere presence of bacteria in nontuberculous infections. The pool of resistant strains in a hospital will increase in proportion to the number of patients receiving an antibiotic. Secondly, it was recommended that bacteriologic cultures be taken before giving an antibiotic, especially for patients with chronic or mixed infections or both. Identification of the unaltered causative organism is essential to proper treatment and makes for more accurate selection of therapy. Thirdly, staphylococcal infections were treated with an appropriate combination of antibiotics. The simultaneous and continuous use of two drugs, to each of which the treated strain is susceptible, will diminish the chance for emergence to predominance of pre-existing resistant mutants.[3]

Preventive Measures in the Operating Room

The deep-seated pathology in the majority of the wound infections suggested that they were, for the most part, seeded in the operating room. Since the nasopharynx is the natural reservoir for the staphylococcus and since the carrier rate for this organism was high, it was urged that two face masks (one over the other) be worn during operations and that they be changed by the circulating nurse every hour and a half during long procedures. The demonstration of lantern slides (Fig. 1 and 2) served to emphasize this point.

A full ten-minute surgical scrub with a G-11 soap, at least for the first case, was advocated. Established principles of meticulous abdominal preparations, gentle atraumatic technics, dry wounds and careful closure were emphasized.

Preventive Measures on the Wards

These were as follows:

The use of face masks for doctors, nurses and patients and the use of gloves during the changing of septic dressings to help prevent the personnel from becoming carriers.

Special septic sets containing the necessary instruments in an aluminum pan covered by a large, sterile, double-ply cloth wrapper. Each set was accompanied by a mask, sterile gloves and a large waxed paper bag for the immediate disposal of soiled dressings. Bags were deposited in a closed container the contents of which were incinerated daily. The set was unwrapped at the bedside, and at the conclusion of the dressing, instruments, gloves and other contaminated materials were deposited in the pan, which was then rewrapped and sent for autoclaving before cleaning and definitive sterilization.

Strict aseptic technique as regards the dressing truck.

Isolation of patients with septic wounds — this proved impractical (local isolation of infected wounds by impermeable occlusive dressings and of the nasopharynx and skin by masks and gloves proved feasible).

Early Control of Wound Infections

One important means of preventing the dissemination of resistant organisms is early control of the infection. A suppurating wound is a source of contamination for other patients, the skin and nasopharynx

FIGURE 1. *Smear Culture of the Inside Surface of the Mask of a Surgeon Who Was a Heavy Nasopharyngeal Carrier after Operation of a Hundred Minutes' Duration, Showing Almost Pure Growth of* Staph. aureus.

of hospital personnel, blankets and air. The localized suppuration commonly called wound infection is a septic breakdown of devitalized tissue, blood clot or serum. Living tissue is only secondarily involved by invasive infection in consequence of contiguity with the retained products of suppuration. Only the hemolytic streptococci appear sufficiently invasive to become established in a wound free of devitalized tissue or blood clot. Antibiotics may mask or modify the severity of wound infection and will control the invasive component surrounding suppurative disease, but seldom if ever cure the suppurative process itself

or prevent local necrosis of fascia. Effective treatment demands removal of the nutritional pabulum upon which bacteria thrive. The minimal therapeutic requirement for major wound sepsis is adequate surgical drainage under appropriate antibiotic protection. Removal of dead tissue and blood clot may then be accomplished by bacterial decomposition or chemical dissolution, which requires weeks to months, or by surgical excision, which is rapid and effective. Conversion of an infected wound into a clean one by immediate drainage and débridement is a practical and safe maneuver under proper antibiotic protection and allows early secondary closure and discharge from the hospital. When applicable, it has proved a highly satisfactory method for prompt and complete control of the infectious process. This procedure was performed for 7 of the major wound infections reported here for 1954 and 1955 and has been successful in a larger group of cases not included in this series. It is contraindicated in elderly or debilitated patients, in cases in which additional anesthesia would be more hazardous than the ravages of sepsis, in the less serious infections that can be controlled in a shorter time by conventional methods and in certain anatomic situations in which proper obliteration of dead space at the time of secondary closure would not be possible.

In major infections not treated by conversion and closure, surgical drainage under strict aseptic precautions was carried out as soon as serious wound suppuration became recognizable — usually on the fourth to the sixth postoperative day. Drained or open suppurating lesions and granulating wounds were treated with sodium hypochlorite or saline packs. Freshly débrided wounds were kept clean pending secondary closure by sterile injections of small amounts of saline solution or appropriate antibiotics in aqueous solution via catheters led out through occlusive waterproof dressings. Once in place, this type of dressing need not be changed until secondary closure is done on the second to the fourth day and is an effective means for preventing recontamination.

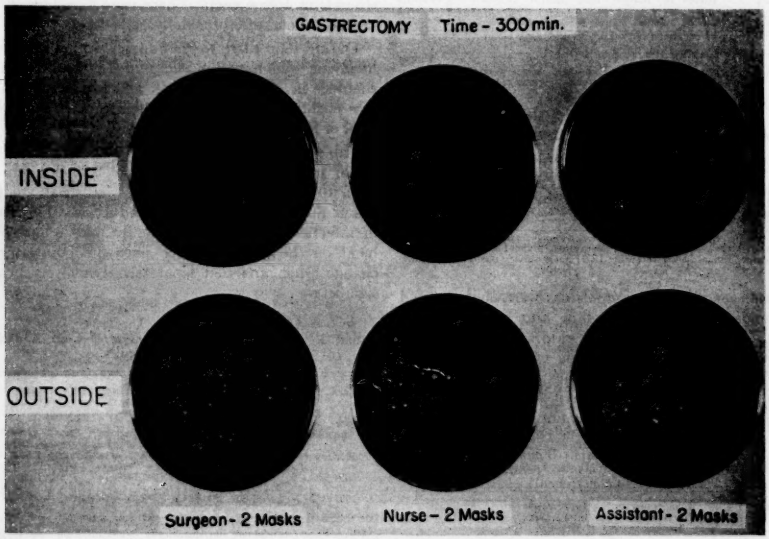

FIGURE 2. *Cultures from the Inside Surface of Inner Masks and the Outside Surface of Outer Masks after an Operation of Three Hundred Minutes' Duration.*

Culture technic was as follows: the mask was held against a blood-agar plate with 568-gm. pressure for ten seconds, a sterile rubber bung, 7 cm. in diameter, being used.

POSTOPERATIVE WOUND INFECTION AND HOSPITAL CARRIER RATES FOR 1954 AND 1955

Material and Methods

All operations were classified according to the method previously described[1] and recorded in the weekly surgical-staff-meeting reports compiled by the residents in charge of the house and private services. All trivial infections, stitch abscesses and inflammatory reactions in wound margins were included. Delayed or masked infections that appeared in the

follow-up clinic or surgeon's office after the patient was discharged from the hospital were also included. The mere presence of *Staph. aureus* in a wound is not an acceptable basis for the diagnosis of staphylococcal infection. This organism can be recovered from the majority of open, unprotected wounds after a week or more of exposure to the hospital environment. In all cases in this study the diagnosis of infection was made on a clinical basis in closed postoperative wounds. Major infections were characterized by tenderness, redness, swelling and increased local heat. Spontaneous or induced drainage of pus or destruction of tissue by bacteria was always present.

Wound infections were classified as major (serious) or minor (trivial) with the use of the criteria outlined in the last report.[1] Classifications were personally checked and discussed at the weekly meetings. Reports were crosschecked with the patients' records and the bacteriology laboratory.

Carrier-rate survey, bacteriologic and penicillin-sensitivity technics were the same as those previously described.[1]

TABLE 1. *Rates of Major and Minor Wound Infections after Group A and B (Clean) Operations.**

SAMPLE STUDIED	1953		1954		1955	
	NO. OF OPERATIONS	INFECTIONS	NO. OF OPERATIONS	INFECTIONS	NO. OF OPERATIONS	INFECTIONS
		%		%		%
House service	429	7.22	326	5.21	321	5.29
Private service	800	2.25	806	1.61	845	0.94
Totals	1229		1132		1166	
Averages		3.98		2.65		2.14

*Analysis shows private service & average percentage rates for 1955 significantly reduced over those for 1953; house-service changes not statistically significant.

TABLE 2. *Percentages of Major Wound Infection after Group A and B (Clean) Operations.**

YEAR	INFECTIONS ON HOUSE SERVICE	INFECTIONS ON PRIVATE SERVICE	AVERAGES
	%	%	%
1953	4.66	1.87	2.85
1954	3.37	0.86	1.59
1955	3.42	0.82	1.54

*Average percentage-rate reductions for 1955 over those for 1953 statistically significant but reflect fundamentally improvement in private service.

RESULTS

Postoperative Sepsis in Clean Wounds

The data presented here are supplementary to those already published,[1] and Tables 1-7 are arranged in the same format and correspondingly numbered. Since the infection rate had progressively increased through 1953, when the new program was started, statistics for that year are again included to afford a ready means of comparison with the present rates.

Significance tests* were applied to all data by Mr. John Alman, director of the Office of Statistical Research Services of Boston University.

During 1954 there were 18 major infections. Lumbodorsal incisions were involved in 6, abdominal incisions in 5, and herniorrhaphies in 2 cases and transthoracic, cervical, craniotomy, breast and skin-graft wounds in 1 case each. There were 12 minor infections — a total of 30 for the year.

During 1955 there were 18 major wound infections involving abdominal incisions in 12 cases, herniorrhaphies in 4 cases and hand and leg incisions in 1 case each. There were 7 minor infections, making a total of 25.

Table 1 shows that the over-all rate for major and minor infections was reduced from 3.98 per cent in 1953 to 2.14 per cent in 1955. Statistical analysis shows this to be a significant reduction. This drop in infection rate is fundamentally due to improvement on the private service since the house-service change when analyzed separately is not statistically significant.

TABLE 3. *Minor Wound Infections after Class A and B (Clean) Operations.**

YEAR	INFECTIONS ON HOUSE SERVICE	INFECTIONS ON PRIVATE SERVICE	AVERAGES
	%	%	%
1953	2.56	0.37	1.14
1954	1.84	0.74	1.06
1955	1.86	0.11	0.60

*Percentage-rate changes not statistically significant from year to year.

Table 2 shows that the rate of major wound infections was reduced from 2.85 per cent in 1953 to 1.54 per cent in 1955. Since major wound infections account for almost all the morbidity, expense and prolongation of hospitalization incurred because of postoperative sepsis, the data in this table represent the crux of the matter. The percentage reductions for the individual services are not significant, but when data from both services are pooled, the level of significance is reached because of a substantially greater number of cases. The over-all improvement is again largely a reflection of the drop in the number of infections on the private service, where the rate of 0.82 per cent for 1955 is gratifying and probably represents nearly maximal attainment. The house-service rate remains over 3 per cent and poses the greatest problem. Studies directed toward its elucidation and further reduction are now in progress.

*Chi-square analysis, or the T test, with the use of the angular transformation, was applied as indicated.[4]

It will be noted that the improvement in the rate of major wound infections took place between 1953 and 1954 directly after the new program came into effect and that there is no significant difference between 1954 and 1955.

Table 3 is supplementary to Table 2 and gives the percentage rates for minor wound infections. Since the percentage increases from 1949 through 1953 were previously shown not to be significant[1] the whole series was reanalyzed from 1949 through 1955. Although the private service shows a slim bit of evidence for improvement, it is believed that the changes in the minor wound series must be accepted as not significant. This substantiates the previous contention that before 1953 the yearly increase in rate was almost entirely due to major wound infections and indicates that the present improvement is due to a reversal of that trend. There have been no statistically significant changes in the rate of minor wound infections over the seven-year period reported.

TABLE 4. *Occurrence of* Staph. aureus *in Flora of Major Wound Infections Cultured from Patients on Private and House Services.**

YEAR	OCCURRENCE IN FLORA		OCCURRENCE AS PREDOMINANT ORGANISM	
	RATIO	PERCENTAGE	RATIO	PERCENTAGE
1953	30:31	96.8	25:31	80.6
1954	15:17	88.2	15:17	88.2
1955	13:16	81.3	9:16	56.2

*Analysis shows 1953 as abnormally high year in comparison with others[1] & indicates return to pre-1953 levels during 1955; percentage reduction for occurrence as predominant organism in 1955 highly significant.

Table 4 shows the occurrence of *Staph. aureus* in the floras of the major wound infections that were cultured. In 3 infections during the last two years no culture was obtained. The left-hand column of the table shows that this organism continues to be present as a component of the floras in a high percentage of cases. The right-hand column shows its occurrence as the sole or predominant organism responsible for the infections. Application of the T test with the use of the angular transformation[4] to the 1953 and 1955 rates indicates a highly significant reduction for its occurrence in the floras and also as a predominant organism. Reanalysis of the series from 1949 through 1953 with the addition of data collected during 1954 and 1955 was carried out. Results show 1953 as an abnormally high year as compared with others, with a return to pre-1953 levels in 1955. During 1955, *Staph. aureus* was the causative agent in 9 of the 16 major infections cultured — an incidence of 56.2 per cent. This is a highly significant reduction and indicates that this type of infection is being encountered less frequently than formerly. Data regarding the occurrence of other bacteria cultured during 1955 are presented in Table 8.

Table 5 shows that, in 1954-1955, 28 of the 33 major infections cultured yielded *Staph. aureus,* that 19 were tested for penicillin sensitivity and that 16 (84.2 per cent) of these were penicillin resistant. In the years 1952-1953, 29 out of 31 strains tested were penicillin resistant (93.5 per cent). These figures suggest that penicillin-resistant strains are being encountered less frequently in the wound infections, but the samples are fortunately so small that the percentage reductions are not statistically significant.

TABLE 5. *Penicillin Sensitivity of* Staph. aureus *Recovered from 33 Major Wound Infections in 1954-55.**

DATUM	NO. OF CASES
Major wound infections	36
Culture performed	33
Staph. aureus found	28
Test for penicillin sensitivity	19
Penicillin-resistant *Staph. aureus* found	16
Penicillin-sensitive *Staph. aureus* found	3

*Although less penicillin-resistant strains found than in 1952-1953 period[1] samples so small that percentage reductions not statistically significant.

CARRIER SURVEY OF PATIENTS AND PERSONNEL

In August, 1953, the hospital carrier rate for *Staph. aureus* was determined, the house surgical floor and operating-room patients and personnel being used as a representative sample. In August, 1955, a survey using the patients and personnel in the same areas was repeated exactly as described previously.[1]

TABLE 6. *Staphylococcal Survey of Nose, Nasopharynx and Hand-Skin Cultures.**

DATUM	1953		1955	
	NO. OF CASES		NO. OF CASES	
Culture on personnel	88		136	
Culture on patients	37		42	
Totals	125		178	
Staph. aureus carrier	124 (99.2%)		134 (75.2%)	
Nose carrier	116		134	
Hand carrier	100		106	

*Carrier rate for 1955 significantly reduced over 1953.

Table 6 compares these surveys and shows that in the samples tested the carrier rate was reduced from 99.2 to 75.2 per cent in the two-year period.

Table 7 shows that the incidence of penicillin-resistant strains in carriers was reduced from 78.5 per cent in 1953 to 62.7 per cent in 1955.

Analysis shows the percentage reductions in Tables 6 and 7 to be highly significant.

Table 9 shows the monthly percentage rates for major and minor infections for 1949, in which the rate was reasonably low, as compared to the last three years. It will be noted that after mid-1954 the

incidence of sepsis was never higher than 2 or 3 per cent for any month except August and December, 1955, when the highest rates occurred.

In August there were 75 clean operations with 4 major and 2 minor infections. *Staph. aureus* was the predominant organism in 5 cases, and a proteus spreader in 1.

In December there were 73 clean operations with 4 major infections and 1 minor. The predominant organisms were Type 3 pneumococcus, in 1 case, *Ps. pyocyaneus* in another case and *Staph. albus* in a third. In 2 cases no culture was taken.

TABLE 7. *Penicillin-Resistant Strains among Carriers.**

DATUM	1953 NO. OF CASES	1955 NO. OF CASES
Nasopharyngeal carriers	116	134
Penicillin-resistant *Staph. aureus*	91 (78.5%)	84 (62.7%)
Penicillin-sensitive *Staph. aureus*	22 (19.0%)	50 (37.3%)
Unsatisfactory test	3 (2.5%)	0

*Percentage reduction of penicillin-resistant strains among carriers from 75.5 to 62.7 significant.

DISCUSSION

In the evaluation of staphylococcal wound sepsis the following points must be kept in mind: in the first place, the staphylococcus has always been a common wound pathogen and in the preantibiotic era was a predominant cause of wound infection[5,6]; secondly, the human nasopharynx and skin are natural reservoirs for *Staph. aureus* — various studies before the days of penicillin showed that 22 to 45 per cent of hospital personnel and patients carried it in the nose and 5 to 21 per cent on the skin[7]; thirdly, outbreaks of staphylococcal wound sepsis, equal in magnitude to those reported here, were known before antibiotics were used and could be traced to individual carriers.[8]

It is obvious, therefore, that there is nothing new about the problem of wound infection owing to staphylococci. It has always existed as a prominent component of the over-all picture of surgical sepsis. In view of the renewed awareness of the problem among surgeons, the question arises whether or not sporadic outbreaks are now generally more severe and frequent than in the preantibiotic era. To show that the general status of *Staph. aureus* wound sepsis is different from that formerly observed for a given hospital, it is necessary to demonstrate an over-all increase in the infection rate owing to this organism over a prolonged period. An elevated rate in itself does not incriminate antibiotic-resistant strains as a contributory factor and might be due to normal seasonal or cyclic variations in the hospital flora or associated with carriers of nonresistant strains. But when an increased rate of staphylococcal infection is found simultaneously with an abnormally high hospital carrier rate of antibiotic-resistant strains and a history of heavy and prolonged use of antibiotics, there is a strong probability that the selective emergence and dissemination of resistant organisms as a result of widespread antibiotic therapy is an important contributory factor. This appears to have been the case in the Massachusetts Memorial Hospitals in 1953. Various workers[9-11] have carried out phage-typing studies of staphylococci from patients and staff indicating that organisms are acquired by crossinfection from other patients and personnel, chiefly the latter.

The data presented here indicate that in the two-year period 1953-1955 there have been statistically significant reductions in the over-all rate of postoperative wound infections, the incidence of sepsis due to *Staph. aureus*, the hospital carrier rate of this organism and the number of penicillin-resistant strains among carriers. It appears likely that this improvement is related in some degree to the preventive measures outlined above, but it is impossible to ascribe it to any one factor. Since mid-1954 there has been but 1 serious outbreak of staphylococcal sepsis, consisting of 5 infections during August, 1955.

TABLE 8. *Occurrence in Flora of Organisms besides* Staph. aureus *in 16 Major Wound Infections during 1955.*

ORGANISM	NO. OF TIMES CULTURED	NO. OF TIMES AS PREDOMINANT ORGANISM
Enterococcus	5	0
Escherichia coli	4	0
Aerobacter aerogenes	4	0
Pseudomonas aeruginosa	4	2
Clostridium perfringens	3	0
Proteus	3	2
Streptococcus, beta-hemolytic	2	1
Streptococcus, alpha-hemolytic	1	0
Streptococcus, nonhemolytic	1	0
Cl. tetani	1	0
Diplococcus pneumoniae	1	1
Bacterioides	1	0
Staph. albus	1	1
Bacillus subtilis	1	0
Paracolon bacillus	1	0
Klebsiella pneumoniae	1	0

This improvement has followed the use of relatively simple and well known measures designed to prevent wound contamination and crossinfection. The importance of the nasopharynx as a carrier site has been stressed, but I am aware that other sources of contamination may be responsible. Duguid and Wallace,[12] for example, have shown that more staphylococci may emanate into the air from a surgeon's skin and clothing as a result of motion and friction dur-

ing an operation than are disseminated by an unmasked sneeze. This poses the question of the relative importance of air "fall-out" contamination versus direct propulsion of bacteria from the masks of the operating team into the wound when there is a high nasopharyngeal-carrier rate among personnel. It also emphasizes the need for further studies to determine the most efficient and practical type of masking — for example, whether masks of impermeable or filtering type are preferable in view of the carrier problem. Also to be kept in mind is the possible role of fecal carriers,[13] blankets, the laundry and various housekeeping factors as sources of contamination. Blowers et al.[2] took much more elaborate remedial measures than those used in the period reviewed above, including floor oiling, chemical treatment of blankets in the laundry, curtailment of movement in the operating room and revision of the air ventilation and filtration system. It is planned to evaluate some of these measures as possible means of further reduction of the house-staff infection rate in the Massachusetts Memorial Hospitals.

TABLE 9. *Monthly Percentages of Major and Minor Wound Infections.*

MONTH	1949	1953	1954	1955
	%	%	%	%
January	0.78	5.22	3.06	0.00
February	0.87	2.15	0.75	2.00
March	2.38	2.34	7.75	0.90
April	2.97	4.46	5.81	1.63
May	0.00	1.12	3.85	2.94
June	0.00	7.14	0.00	1.00
July	1.68	6.19	0.00	1.00
August	1.32	3.75	2.13	8.00
September	0.00	3.37	0.00	1.00
October	1.15	2.69	1.26	1.90
November	0.00	4.71	2.00	2.40
December	1.27	4.65	2.60	6.80

Among other things, host factors are influential determinants of wound sepsis. The general condition of the patient and the technical management of the wound are important. The presence of excessive devitalized tissue, blood clot or serum invites infection. Regarding the relatively high rate of sepsis on the house service as compared to the private, host factors probably play an important part. Since the development of medical-insurance plans and Veterans Administration hospitals, the character of patients on the house service wards has changed. The majority of them are in the older age group and are frequently suffering from degenerative diseases or metabolic aberrations in addition to a serious surgical lesion. Young, good-risk surgical patients with uncomplicated diseases are seldom seen on the wards at present. Biweekly checks during April, 1956, showed the average age of house-service patients to range from fifty-nine to sixty-three years. A recent spot check showed the average age of the private surgical patients to be forty-six. The average age of all patients with major wound infections was fifty-two years during 1954 and fifty-nine years during 1955.

Although prophylactic administration of antibiotics in civilian surgery is warranted under special circumstances[14-19] there is some question of the wisdom of applying this principle to all "clean" operations.

SUMMARY AND CONCLUSIONS

The problem of wound infection owing to *Micrococcus pyogenes* (var. *aureus*) is an old one and has always been a prominent component of the over-all picture of surgical sepsis. The extensive use of antibiotics in a hospital, by virtue of the emergence and dissemination of resistant strains, may intensify this problem to such an extent that the over-all infection rate is increased.

Prevention of postoperative staphylococcal sepsis depends upon meticulous wound management and elimination of crosscontamination from patients to personnel and thence to other patients. Emphasis is placed upon well established surgical and antiseptic technics rather than prophylactic antimicrobial therapy.

Reservation of the use of antibiotics for the treatment of established infections and the judicious use of appropriate combinations of drugs may curtail and delay the emergence of resistant strains of staphylococci. The prophylactic administration of antibiotics in civilian surgery is reasonable and helpful under certain special circumstances, but the indications are limited and need further clarification. When adopted as a routine measure before and after all "clean" operations, it may be more harmful than beneficial.

Data on the rate of clean wound infections at Massachusetts Memorial Hospitals for the period 1949-1955 are reviewed. A gradually increasing infection rate during the five years before 1954 is attributed largely to a high hospital carrier rate of penicillin-resistant *Staph. aureus* as a result of widespread use of this antibiotic.

During the last two years the hospital carrier rate of *Staph. aureus* and the incidence of penicillin-resistant strains in carriers have been significantly lowered, and the rate of postoperative wound infections has been reduced by almost half since the institution of a relatively simple program for the prevention of crosscontamination and judicious use of antibiotics.

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SYSTEMIC TREATMENT OF PRIMARY TUBERCULOSIS*

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TODAY, various drugs are available that have proved very active against tubercle bacilli. It is known that the sooner they are resorted to, the more effective they will be. It is therefore more than ever necessary to diagnose any form of tuberculosis as early as possible since a delay in the recognition of severe tuberculous manifestations can entail heavy consequences. But, in my opinion, this applies also to primary tuberculosis, even of the most benign type, which should be diagnosed as soon as feasible.

The important problem at present is whether all cases of primary tuberculosis — whether latent or not — should be treated as soon as they are recognized. It is extremely difficult to answer this question. Further studies are required, but, as long as the problem has not been settled, physicians must decide in each case, well aware that they are assuming as heavy a responsibility in deciding not to treat a child as they do when they prescribe antituberculous drugs.

THEORETICAL ARGUMENTS IN FAVOR OF TREATMENT

It is well known that tuberculous infection brings forth one or several primary nodes associated with a more or less voluminous adenitis. Moreover, any tuberculous invasion entails a latent miliary dissemination. In their study of 235 children with primary tuberculosis Monbrun and Lavat[1] found choroidal tubercles, which are the indisputable proof of an inapparent dissemination, in 6 per cent of the cases. The future of these children will depend upon the evolution of the minimal and inapparent dissemination in the lung and in other organs, as well as upon the evolution of the pulmonary lesions and of the mediastinal adenitis.

The necessity of applying treatment to recently contaminated children would be established if it were demonstrated that it is thus possible to prevent generalized, acute tuberculosis, secondary bone and other localizations and, lastly, chronic pulmonary tuberculosis in adolescents and adults. Many facts tend to show that all these localizations are more or less consequences of the initial infection. Miliary infection and meningitis appear mainly during the year after contamination. Bone and visceral lesions are a belated revival of a latent hematogenous dissemination during the primary stage. From the work of Medlar[2] and of Terplan[3] it may safely be inferred that 86 to 97 per cent of chronic tuberculosis occurring under thirty years of age resulted from the evolution of primary lesions whereas only 3 to 14 per cent could perhaps be regarded as the result of reinfection.

Moreover, the remarkable action of antituberculous drugs on recent lesions is well known; they prevent bacterial proliferation, they sometimes destroy the organisms, and it has recently been shown that they may sometimes modify profoundly the characteristics of the surviving bacilli, so as to render them less virulent when they become more or less resistant. Under existing conditions, complete sterilization of the human organism by means of treatment does not seem possible. The bacilli that survive in spite of the treatment maintain tuberculin allergy and also immunity against reinfection. What may be expected from treatment is the emergence of a residual, minimal, nonevolutive focus, latent allergy and an immunity, inducing a lesion similar to that which is found in the majority of the adults who, infected by Koch bacillus, never contract tuberculous disease, and, on the other hand, resembling the lesion deriving from the inoculation of an attenuated bacillus — the BCG, for example. Thus, it can be hoped that, by the treatment of tuberculosis from its very onset, the pulmonary disease of adult years, which is the real challenge of tuberculosis, can be prevented. I have faith that future studies will prove the validity of this conception. If it is so, it will prove the analogy between

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tuberculosis and syphilis. When syphilis is treated at the time of the chancre, all the late complications of the disease are prevented (these complications being recognized as direct consequences of the minimal initial lesion). Similarly, pediatricians, applying the proper treatment to tuberculosis at its onset, will be rewarded by the prevention of all the late localizations of the disease. The validity of these views will only be checked in a somewhat distant future.

The action of chemotherapy and antibiotics is inseparable from spontaneous reactions of the infected human organism. It should therefore be decided at what stage treatment should be applied with the greatest chances of success. This question has not yet been solved despite clinical and experimental investigations. Should treatment be given during the preallergic period? This has been done by Lelong,[4] who has treated, before conversion of their tuberculin tests, newborn infants, probably contaminated by their mothers. Experimentally, Ferebee and Palmer[5] have found that guinea pigs, receiving isoniazid before and for ten weeks during virulent infection, are protected for at least twenty-six weeks. But Schmidt,[6] in experiments with a longer period of observation, has protected with isoniazid monkeys submitted to tuberculous contacts, and has seen the disease appear after the treatment had been discontinued, in the absence of any new tuberculous contact.

Is it better, then, to treat the patient at the hyperergic stage when allergy appears, or later? Without being able to supply supporting evidence, I believe that treatment must be initiated during the hyperergic period, which is characterized by intense reactions of the infected organism.

Consequently, the tracing of the penetration of the bacillus into the body will have to be most careful. The periodic checking of the tuberculin test in any community of children and the individual search for allergy in every sick child (whose symptoms are not demonstrative) is absolutely indispensable. The recourse to that excellent method of individual and collective prophylaxis must be intensified. One should therefore strongly support the campaign launched by the National Tuberculosis Association in favor of a more extensive use of tuberculin tests.

Risks of Tuberculous Disease

Data regarding the risk run by the recently infected child are reported herewith.

Frölich's[7] statistics are among the most accurate of the first ones recorded. They cover 1830 school-age children of Oslo, Norway, who had a positive tuberculin test at the age of seven in 1912. In 1925, at the age of twenty, 87.8 per cent seemed untouched by tuberculous manifestation. This means that between the age of seven and twenty years, 12.2 per cent displayed tuberculous manifestations, involving the lungs (4.5 per cent), the pleura (3.9 per cent), the bones, joints and lymph nodes (3.4 per cent) and the meninges (0.38 per cent).

Later, Meyer[8] found comparable figures in a group of 2146 children followed from 1929 to 1944. Heimbeck[9] noted a rate of 0.5 per cent of pulmonary tuberculosis during the first year after contamination in children under twelve; Malmros et al.[10] found a figure of 10 per cent in adolescents. Ustvedt[11] reported pleural effusion in 3 per cent and extrathoracic tuberculosis in 1 per cent shortly after the infection.

In the United States, Tsai and Bashe,[12] in a survey of 600 cases, tabulated, shortly after tuberculous invasion, miliary tuberculosis in 5 per cent of the cases, meningitis in 2.4 per cent, bone tuberculosis in 3.2 per cent and a pulmonary cavity in 4 per cent. The figures reported by Lincoln[13] are even higher.

The French statistics established in collaboration with Brissaud[14] and by Lotte and Rouillon[15] provide similar results. The risk of early tuberculous meningitis as related to the number of contaminations is 0.33 per cent; that of chest tuberculosis is 4.5 per cent. Grossly, out of 1000 school-age children contaminated at the age of seven years, on the average more than 120 present a tuberculous localization before the age of twenty, including pleural effusion in 30, pulmonary involvement in 45 and meningitis in more than 3. In addition these statistics concern only persons under the age of twenty.

Elements of Prognosis

Age

The child's age is a factor of major importance. The severity of tuberculosis in very young children is well known. In children under three years, morbidity, for extrapulmonary tuberculosis only, rises to 5 to 10 per cent, with a mortality of 3 per cent, owing to the high incidence of meningitis in that group. The risk is greater in infants. Bernard and Debré,[16] twenty-five years ago, found a mortality of 24 to 25 per cent among infected infants under six months and one of 5 or 6 per cent in the age group six to eighteen months. These figures (without treatment) have changed but little.

Tuberculosis is also especially severe after the age of thirteen years in girls and after fifteen in boys. The incidence of pulmonary tuberculosis, which is 0.3 per cent yearly until the age of thirteen, rises suddenly, and, if primary tuberculosis occurs after the age of thirteen, the yearly incidence reaches 2 and 3 per cent during the three or four following years, thus realizing a total morbidity of over 10 per cent. It is at this very time of life that chronic pulmonary tuberculosis stems from the evolution of primary lesions and should be prevented by routine treatment of the initial tuberculosis.

Importance of Contact

A factor that also accounts for the severity of some

cases is the importance of contacts. Holmdahl[17] found familial contamination in 13.4 per cent of cases of common, uncomplicated tuberculosis and in 24.7 per cent of cases of complicated primary tuberculosis.

In tuberculous meningitis[18] familial contagion was noted with a significant frequency, since in 418 cases of acute tuberculosis, including 293 of meningitis, it was found that the child had been contaminated by the father or the mother in 34 per cent of the cases.

Many years previously, it had been shown[19] that the severity of primary tuberculosis in the infant was closely related to the intimacy of the contact and probably to the amount of bacilli spread by the contaminator. An attempt had been made to establish the relation between the severity of primary tuberculosis and the age of the child, the importance and the duration of the contact. Contamination in the family and in public places was always contrasted.

Features of Tuberculous Invasion

Can one find elements of prognostic value in the very features of primary tuberculosis? Ustvedt and Johannesen observed a slightly higher morbidity in children affected with erythema nodosum in the course of primary tuberculosis than in others. This fact was not confirmed by Meyer,[8] who believed that a high erythrocyte sedimentation rate, during the early phase of the disease, forecasts a higher incidence of pulmonary tuberculosis in subjects over eighteen years. The finding of bacilli in gastric-lavage samples would give the same indication.

There was closer agreement on the value of the x-ray findings. Holmdahl[17] saw the development of pulmonary tuberculosis twice as frequently when he had noted the primary focus on x-ray films. But this observation was made in too few children to have statistical value.

In children ranging from three to thirteen years of age the over-all prognosis is good. Nevertheless, the lack of clinical or roentgenologic manifestations does not permit an absolutely favorable prognosis.

To sum up, it is possible to recognize the severity of certain elements of prognosis, but not to conclude, if these are lacking, that the course of primary tuberculosis will be favorable. Although the risk is less under good conditions, it is not negligible and, above all, can never be foreseen.

Indications

It is generally agreed in France to give treatment in the following conditions: infants under two years of age; children at the puberty and postpuberty periods; tuberculous invasions with general symptoms, such as fatigue, fever, acceleration of the sedimentation rate, abnormal x-ray film or erythema nodosum; and children who have been exposed to massive contamination.

The problem of treatment is far more difficult in school children with recent tuberculin allergy but no clinical or radiologic signs. Is the treatment necessary, since primary tuberculosis is usually a curable disease that generally confers immunity?

On the other hand, has not experience been gained from the study of streptomycin that the treatment of primary tuberculosis did not always prevent the subsequent development of other tuberculous lesions? Did it favor the appearance of resistant organisms? Are the risks the same with isoniazid?

There is good evidence of a greater efficiency of isoniazid. The drug spreads better in the whole body and reaches tuberculous lesions. During the evolution of isoniazid-treated miliary forms, meningeal localizations or secondary involvement of nodes and joints, so frequent in streptomycin-treated cases, are no longer seen.

Therefore, the activity of isoniazid favors its use for routine treatment of primary tuberculosis. But, instead of framing hypotheses, it would be better to try to obtain a clear view of the position — in a word, to treat children and compare them with untreated controls.

To solve the problem, extensive studies are required. They have been undertaken in New York City on the initiative of Dr. E. Lincoln. In France the National Institute of Hygiene, under the leadership of Professor Bugnard and with the assistance of the Social Security Services, is conducting an inquiry that, at the end of 1955, was based on 3943 children, 1646 of whom were treated with isoniazid combined with para-aminosalicylic acid. The 2297 other children will remain untreated and will be taken as controls.

The distribution by age groups in these 3943 cases is as follows: 310 children under two, 688 two to four, 1835 five to nine, 840 ten to fourteen, 115 fifteen to twenty and 103 over twenty years of age, in addition to 52 whose cases have not yet been fully investigated.

Only recent primary tuberculosis cases are retained for study — that is, the cases for which the tuberculin reaction was known to be negative less than six months before the beginning of treatment.

The inquiry is still in progress, and no final conclusion can yet be drawn. All I can offer is a summary of the observations made by my associates[20] on the patients under our care:

The efficiency of treatment on the general status and on the sedimentation rate is obvious (Table 1).

X-ray evolution varies from case to case (Table 2). If the pulmonary or mediastinal picture was normal when the treatment was initiated, no modification occurs during its course.

Segmental opacities are definitely but slowly modified.

Nonsegmental opacities disappear in the course of treatment. The result obtained in this last category seems of particular importance, since it refers mainly to pulmonary lesions from which progressive pulmonary tuberculosis may derive.

The evolution of bronchial lesions, especially fistula, does not seem to be influenced by treatment.

Regarding bacterial evolution, it is to be noted that bacilli usually disappear after the third month of treatment. However, bacilli may be found later. In these cases, a nodular fistula is generally found. The organisms have usually retained their susceptibility to para-aminosalicylic acid and isoniazid.

Table 1. *Evolution of Erythrocyte Sedimentation Rate in Treated and Untreated Cases of Primary Tuberculosis.*

Treatment	No. of Cases	Cases with Sedimentation Rate below 10 Mm./Hr.			Cases with Sedimentation Rate of 10-30 Mm./Hr.			Cases with Sedimentation Rate above 30 Mm./Hr.		
		Initial value	After 6 mo.	After 12 mo.	Initial value	After 6 mo.	After 12 mo.	Initial value	After 6 mo.	After 12 mo.
		%	%	%	%	%	%	%	%	%
Para-aminosalicylic acid & isoniazid	100	30	84	90	40	10	9	30	6	1
Para-aminosalicylic acid alone	76	21	76	84	33	19	11	46	5	5
No drug treatment	72	21	39	64	51	51	29	28	10	7

It is too early to try to compare the occurrence of postprimary tuberculous localizations in treated and untreated children. The observations must be confined to reporting data from a preventorium near Paris run by one of my associates, Dr. Hanoteau: among 1062 untreated children, between July, 1948, and July, 1955, pleuritis occurred in 44, miliary tuberculosis in 1, meningitis in 3 and progressive pulmonary tuberculosis in 13. During the same period, among 600 children treated with para-aminosalicylic acid alone, or with that drug combined with isoniazid, there was no pleuritis, no miliary tuberculosis, no meningitis and 1 case of progressive pulmonary tuberculosis.

Table 2. *X-Ray Evolution in Treated and Untreated Cases of Primary Tuberculosis.*

Results after 12 months during which:
— 100 children received PAS + INH
— 110 children received PAS alone
— 110 children received no drug treatment

X-Ray Finding	Improvement after 12 Mo.		
	Patients given para-amino-salicylic acid & isoniazid	Patients given para-amino-salicylic acid alone	Patients given no drug therapy
	%	%	%
Lymph-node enlargement Voluminous lymph nodes	77	77	34
Segmental opacities	88	88	43
Nonsegmental opacities	100	59	22
Pleuritis	100	96	94

Mode of Treatment

Isoniazid combined with para-aminosalicylic acid is used. The former is given in a daily dosage of 10 to 20 mg. per kilogram of body weight in two doses, without exceeding a total of 400 mg. per day. For infants under two years of age, 20 to 30 mg. per kilogram is given, without exceeding 10 mg. per kilogram in one dose.

To prevent bacterial resistance para-aminosalicylic acid is given in a dosage of 30 cg. per kilogram of body weight in one or two doses per day. Contrary to what is observed in adults, this drug is readily accepted by children, without gastrointestinal intolerance.

The treatment must be uninterrupted and long lasting. In my opinion the long duration of chemotherapy is essential: at least eight to ten and never shorter than six months.

In the early days of the treatment of acute miliary tuberculosis and tuberculous meningitis, I had warmly recommended prolonged treatments, because in my experience they prevented possible relapses. The importance of the duration of treatment in all tuberculous localizations, especially in pulmonary tuberculosis, has gradually been acknowledged. It is believed that these general principles should be scrupulously respected if the prophylactic action (which is to be achieved by means of the systemic treatment of primary tuberculosis) is to be obtained.

No therapeutic accidents have been noted in treated children. The ease with which treatment is administered and tolerated is of importance, for it makes it possible to apply it without difficulty to a large number of children.

Streptomycin is no longer given; its administration is more difficult and there are no experimental or clinical data to demonstrate a superiority of the isoniazid and streptomycin over the combined treatment described above. It is preferable to keep streptomycin in reserve, in the event that accidents subsequently develop.

Summary and Conclusions

It may be said that treatment of primary tuberculosis has already proved efficacious in preventing pleuritis and meningitis, and in clearing the pulmonary lesions. The action on lymph nodes and atelectasis is less apparent, but by no means negligible. The longer the period of observation, the more marked the differences between treated children and controls.

It should be emphasized that all these are preliminary remarks. To reach conclusions, it will be necessary to compare after many months and after many

years the state of health of treated and untreated people. In the meanwhile, it is believed that, in view of the uncertainty that the future holds in store for each case, it is preferable to give treatment. Of course, this procedure may seem to require too much trouble for the sake of avoiding slight individual risks; yet this is more or less what is done when all children are vaccinated against diphtheria, tetanus, whooping cough or smallpox.

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AGRANULOCYTOSIS ASSOCIATED WITH CHLORPROMAZINE THERAPY

Report of a Case and Review of the Literature

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STUDIES concerning the clinical use of chlorpromazine (10 - [gamma - dimethylaminopropyl] - 2 - chlorophenothiazine) in various medical and psychiatric disorders were begun in 1951 in Europe. Since 1954 chlorpromazine has been used in increasing frequency in this country, the most common indications being mental disorders and nausea and vomiting.

In the use of chlorpromazine the side effects encountered early were relatively mild in nature: drowsiness, nasal congestion, dermatitis, photosensitivity, transient hypotension, tachycardia, constipation, hypothermia, fever and Parkinsonism. Later, more troublesome side effects were described: jaundice of an obstructive type and agranulocytosis. Fortunately, the frequency of the last mentioned complications is not great.

In this hospital chlorpromazine has been used in mentally ill patients since the spring of 1954. More than 700 patients have received this drug. To date 10 cases of obstructive type of jaundice due to chlor-

TABLE 1. *Hemograms before, during and after Agranulocytosis.*

DATE	RED-CELL COUNT	HEMOGLOBIN	WHITE-CELL COUNT	NEUTROPHILS	EOSINOPHILS	BASOPHILS	LYMPHOCYTES	MONOCYTES	MISCELLANEOUS FINDINGS
	X10⁶	*gm./100 ml.*	*X10³*	%	%	%	%	%	
11/17/1955	3.6	12.0	6.9	—	—	—	—	—	—
1/ 4/1956	2.8	8.3	0.8	—	—	—	100	—	—
1/ 6/1956	3.4	9.4	0.9	—	—	—	98	1	Prolymphocytes, 1%
1/ 8/1956	3.8	11.2	1.1	3	—	—	92	2	Prolymphocytes, 3%
1/10/1956	3.9	13.4	2.5	20	2	—	66	12	—
1/14/1956	5.0	14.2	7.35	60	—	—	29	8	Disintegrated forms, 2% Unidentified forms, 1%
1/26/1956	4.1	13.7	6.25	65	—	1	32	2	—

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promazine have been observed. In 5 cases the jaundice subsided in less than four months; in the other 5 it persisted for four to six months and longer. No deaths resulted.

Agranulocytosis as a complication appears to be even less frequent than jaundice. Its seriousness, however, makes it the most important consideration in the use of this drug. To determine the frequency and outcome of this complication the published case reports are of value.

TABLE 2. *Differential Count of Cells in the Sternal Bone Marrow during and after Agranulocytosis.*

CELLS	JAN. 4	FEB. 2
Polymorphonuclear leukocytes	—	45
Band forms	—	70
Metamyelocytes	—	28
Myelocytes	1	25
Promyelocytes	—	3
Blast forms	10	—
Eosinophilic polymorphonuclear leukocytes	—	2
Eosinophilic band forms	—	2
Eosinophilic metamyelocytes	—	2
Eosinophilic myelocytes	—	2
Lymphocytes	81	17
Young lymphocytes	2	—
Monocytes	—	1
Plasma cells	6	2
Normoblasts A	18	15
Normoblasts B	79	36
Normoblasts C	2	0
Erythroblasts	1	1
Megakaryocytes	Present	Present
	200 cells counted	251 cells counted

Among more than 700 patients treated with chlorpromazine in this hospital, only 1 case of agranulocytosis has occurred. However, we have observed 2 additional patients in whom malaise, fever, sore throat with ulceration and decrease of granulocytes in peripheral blood appeared. With prompt discontinuation of the drug these findings returned to normal within a week.

CASE REPORT

S. H., a 62-year-old housewife, was admitted to the hospital on November 17, 1955, with complaints of agitation, ideas of reference and suicidal tendencies. The diagnosis of involutional psychotic reaction was made. Treatment with chlorpromazine, 25 mg. 4 times a day by mouth, was started on November 22. On December 4 oral administration of 50 mg. at bedtime was added. No other medication was given, except occasionally an aspirin for headaches.

In June, 1938, she had been successfully treated with radium and x-rays for carcinoma of the cervix uteri. In October, 1939, she had had infectious hepatitis. In June, 1946, nephrectomy on the right was performed because of hydronephrosis due to a "kinked" right ureter. In November and December, 1953, she was treated for varicosities and cellulitis of the lower extremities. During November, 1955, the symptoms of mental disorder appeared.

On January 3, 1956, she was transferred to the Medical Service because of sudden onset of fever and "sore throat." She appeared acutely ill. The temperature was 104°F. by rectum, the pulse 120, and the respirations 24; the blood pressure was 110/80. The mucosa of the isthmus faucium and pharynx was reddened and covered with dry, yellowish mucus. The cervical lymph nodes were enlarged bilaterally. The lungs were clear to percussion and auscultation. No palpable hepatosplenomegaly was present. Gynecologic and roentgenologic examinations gave no evidence of localized or metastatic cancer. A hemogram on January 4 showed anemia and a white-cell count of 800, all of which were lymphocytes (Table 1), with 0.1 per cent reticulocytes. Bleeding and clotting times were normal. The sedimentation rate was 36 mm. in 1 hour (Westergren method). Platelets numbered 300,000 per cubic millimeter. A stool was negative for occult blood. Urinalysis showed a ++++ test for albumin, with rare white blood cells in the sediment. The differential count of 200 cells of the sternal bone marrow showed almost complete suppression of the granulocytic series (Table 2).

The diagnosis of agranulocytosis was made. Since the hemogram before the administration of chlorpromazine in November, 1955, was within normal limits (Table 1) this drug was considered to be the only apparent causative agent and therefore immediately discontinued. Penicillin was started in doses of 600,000 units intramuscularly twice a day for a period of fourteen days, followed by half that dose for six more days. Ascorbic acid, 800 mg. daily, was given by mouth for 3 weeks. Transfusions totaling 1.5 liters of whole blood were given during the 1st 2 days. No other medication was added. On the 4th day of the illness 10 small, sharply demarcated ulcerations were noted on the lips, hard palate and anterior pillar. On the same day monocytes reappeared in the peripheral blood. Two days later segmented neutrophils reappeared, and from that time on, the hemogram showed rapid improvement. Eleven days after the onset of the disease, the hemogram was normal, remaining stable and within normal limits (Table 1). The ulcers of the mouth and throat disappeared at the same time. The aspiration of sternal bone marrow was repeated on February 2, the smear showing good maturation of white-cell and red-cell series (Table 2).

On February 2 the patient was sent back to the Psychiatric Service fully recovered from the agranulocytosis.

DISCUSSION

Table 3 summarizes 21 cases of agranulocytosis associated with chlorpromazine therapy reported in the literature; some of the reports were incomplete. In several cases other drugs, some of them "white cell granulocyte reactors,"[16] were used concomitantly with chlorpromazine. Therefore, the evidence in all the reported cases is not equally conclusive, but it is still convincing enough for chlorpromazine to be considered the offending agent.

Most of the patients received chlorpromazine for treatment of mental disorders. The age varied: the youngest patient was thirty and the oldest seventy-eight years; the average age was fifty-seven years. All were females. In all but 2 cases the daily dosages were 320 mg. or less. The route of administration was oral, except in 1 case, in which one dose was given intramuscularly. The duration of chlorpromazine administration varied from eighteen to sixty-seven days, with an average of forty-three days. In all but 1 case the peripheral blood showed severe

leukopenia (white-cell counts of 200 to 2300), with complete or almost complete disappearance of granulocytes. The case reported above also showed anemia.

Of 21 cases of agranulocytosis reported 8 were fatal. In most cases death occurred a few days after recognition of agranulocytosis. Half the patients who died had additional complications from the use of chlorpromazine: 3 were jaundiced; and 1 had hypo-

TABLE 3. *Cases of Agranulocytosis Associated with Chlorpromazine Therapy.*

SOURCE	AGE OF PATIENT	SEX OF PATIENT	DIAGNOSIS	CHLORPROMAZINE THERAPY			DRUGS USED CONCOMITANTLY
				DAILY DOSE	DURATION	TOTAL AMOUNT	
				mg.	*days*	*gm.*	
Lomas[1]	69	F	Agitated depression	150 (orally)	40	6.0	Chloral
Munch-Petersen[2]	71	F	—	—	48	10.6	—
Giacobini & Lassenius[3]	57	F	—	—	45	—	Promethazine (antihistaminic)
Boleman[4]	63	F	Agitated depression	30-320 (orally)	67	—	Phenobarbital; phenolphthalein.
Prokopowycz[5]	63	F	Presenile brain disease	100-150 (orally)	53	—	Benadryl
Tasker[6]	38	F	Hysteria & maniacal state	75-150 (orally)	41	5.475	—
Hodges & LaZerte[7]	67	F	Dermatitis	50 (orally)	22		Cremothalidine
			Postoperative nausea	10 (intramuscularly)	1	1.11	
Moyer[8]	(1 patient)		—	1000 (orally)	—	—	—
Pollack[9]	(1 patient)		Mental disorder	—	—	—	—
Barsa & Kline[10]	(1 patient)		Mental disorder	—	42	—	Reserpine
	(1 patient)		Mental disorder	—	42	—	Reserpine
Forman & Ide[11]	73	F	Agitation	100-200 (orally)	55	—	Doriden
Goldman[12]	60	F	Involutional psychosis	150-300 (orally)	53	—	—
	30	F	Paranoid schizophrenia	150-300 (orally)	44	—	—
	34	F	Schizophrenia	150-600 (orally)	44	—	—
	(1 patient)		—	—	—	—	—
Rotstein et al.[13]	52	F	Depressive reaction; chronic anxiety.	75-150 (orally)	39	—	Seconal; aspirin; acetophenetidin; anacin.
	(1 patient)		—	—	42	—	—
Yules & Baker[14]	78	F	Arthritis	100 (orally)	40	—	Digitoxin; aspirin; Gantrisin.
Theriault[15]	38	F	Paranoid schizophrenia	300 (orally)	18	—	—
Present report	62	F	Involutional psychotic reaction	100-150 (orally)	42	5.7	Aspirin

tension. Only 1 patient of 13 who recovered suffered from jaundice in addition to agranulocytosis; recovery from the agranulocytosis took place within two weeks in the majority of cases.

For the treatment of agranulocytosis antibiotics were used in all cases. Seven patients also received steroids (cortisone and ACTH). Among these 7, there were 3 deaths.

TABLE 3 *(Concluded).*

SOURCE	AGRANULOCYTOSIS			OTHER SIDE EFFECTS	TREATMENT OF AGRANULOCYTOSIS	COURSE OF AGRANULOCYTOSIS
	WHITE-CELL COUNT	NEUTROPHILS	LYMPHOCYTES			
		%	%			
Lomas[1]	680	11	—	—	Penicillin; cortisone.	Recovery within 16 days
Munch-Petersen[2]	800	14	—	—	Penicillin; folic acid; blood.	Recovery within 9 days
Giacobini & Lassenius[3]	900	22	—	—	Penicillin; blood.	Recovery within 2 wk.
Boleman[4]	525	—	100	—	Penicillin; whole blood; streptomycin.	Death within 2 days
Prokopowycz[5]	1500	—	70	Skin rash; hypotension.	Penicillin; streptomycin.	Death within 2 days
Tasker[6]	900	10	90	Dermatitis; jaundice.	Penicillin; oxytetracycline.	Death within 7 days
Hodges & LaZerte[7]	12,200	—	95	Jaundice	ACTH; oxytetracycline; streptomycin.	Death within 3 days
Moyer[8]		(Agranulocytosis)		—	—	Death
Pollack[9]		(Agranulocytosis)		—	—	Recovery
Barsa & Kline[10]		(Agranulocytosis)		—	—	Recovery within few wk.
		(Agranulocytosis)		—	—	Recovery within few wk.
Forman & Ide[11]	750	—	100	—	Penicillin; tetracycline (panmycin); cortisone; ACTH.	Death within 12 days
Goldman[12]	2300	—	96	Dermatitis	Penicillin; ACTH; aspirin.	Recovery within 10 days
	1700	—	93	—	Penicillin; Pyribenzamine; ACTH; whole blood; tetracycline.	Recovery within 10 days
	1800	—	98	—	Penicillin; tetracycline; aspirin; ACTH.	Recovery within 10 days
		(Agranulocytosis)		—	—	Death within 3 days
Rotstein et al.[13]	550	—	100	Jaundice	Penicillin; tetracycline; neomycin; streptomycin; Mysteclin; Mycostatin.	Recovery within 10 days
		(Agranulocytosis)		—	—	Recovery
Yules & Baker[14]	200	—	99	—	Penicillin	Recovery within 10 days
Theriault[15]	450	—	100	Jaundice	Chlortetracycline; whole blood; cortisone.	Death within 1 mo.
Present report	800	—	100	—	Penicillin; ascorbic acid; whole blood.	Recovery within 11 days

Summary and Conclusions

A case of agranulocytosis associated with chlorpromazine therapy is reported. The patient received 5.7 gm. of chlorpromazine in forty-two days. The daily dosage was 100 to 150 mg. by mouth.

In the 21 cases reported in the literature 13 patients recovered, and 8 died (a mortality of 38 per cent).

The concomitant occurrence of jaundice and agranulocytosis as complications of the use of chlorpromazine is highly fatal.

Careful clinical and laboratory observation of patients receiving chlorpromazine is essential to prevent occurrence of agranulocytosis and consequently to eliminate deaths from this cause.

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A PRELIMINARY EVALUATION OF TRANSVENTRICULAR AORTIC COMMISSUROTOMY WITH AN IMPROVED DILATOR*

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AORTIC commissurotomy now may be considered for any patient disabled by stenosis of the aortic valve. Previous reports by others[1-6] have dealt primarily with analysis of operative mortality by different approaches and subjective evidence of improvement in survivors. The purpose of this report is to describe our initial experiences in surgical treatment with improved instrumentation, and to evaluate early results by both subjective and objective criteria.

Methods and Material

Fifteen patients underwent aortic-valve surgery by one of us (K.A.M.) utilizing a transventricular approach with a modified Bailey dilator. The chief modification of this instrument (Fig. 1) is the small size of the shaft (7/32 inch), which is 1/32 inch greater than half the diameter of the original Bailey instrument and a third of the area. Although expanding to a comparable 3 cm. when fully opened, the dilator head collapses completely into this small shaft when closed. Thus, only a small incision is required for insertion of the closed instrument into the left ventricle. Other modifications have resulted in strength equaling, if not surpassing, that of the Bailey dilator.‖

Criteria for operation were demonstration of aortic stenosis as the predominant lesion and presence of significant disability. Specific contraindications were recent myocardial infarction and bacterial endocarditis.

Figure 1. *Aortic Dilator (Head Fully Expanded).*

Age, valvular lesions, severity and duration of

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‖This instrument was designed and manufactured by Mr. Wayne E. Quinton, of the Medical Instrument Shop, University of Washington.

symptoms and degree of disability in each patient are shown in Table 1. Standard chest films indicate the degree of cardiac enlargement in each patient (Fig. 2). The average age was forty-seven years (range, twenty-nine to sixty-two years); 5 patients were over fifty-seven years of age. All but 2 patients were males. Etiology was considered to be rheumatic heart disease in almost all cases; none were thought to be congenital lesions. All patients were either Class 3 or 4 (functional classification of New York Heart Association). Ten patients had only aortic stenosis, whereas 5 also had significant mitral stenosis or aortic insufficiency or both (Table 1, Cases 11-15).

Objective evaluations before and after surgery included direct arterial-pressure recordings and a standard exercise-tolerance test[7] in the majority (Table 2). One patient (Case 11) has not been evaluated since operative convalescence, although he is known to be well enough to attend barber school. The follow-up period in survivors has ranged from three to eleven months, averaging six and four-tenths months.

Results

Operative Experience

There were no operative or immediately postoperative deaths in these 15 patients. Serious arrhythmia did not occur at operation. Bleeding from the ventriculotomy wound after removal of the instrument created no problem. The average blood loss was approximately the same as that for mitral commissurotomy. In no case was either procaine injected into the ventricular wall or a purse-string suture placed about the ventriculotomy. In some cases no suture was necessary at the ventriculotomy site after removal of the instrument. Postoperative neurologic abnormalities attributed to cerebral emboli occurred in 3 patients, none with serious permanent residua. Subsequently, temporary occlusion of the left carotid and innominate arteries has become a routine part of the operative procedure. Further embolism has not been manifest.

Direct pressures in the aorta and left ventricle immediately before and after commissurotomy in Case 2

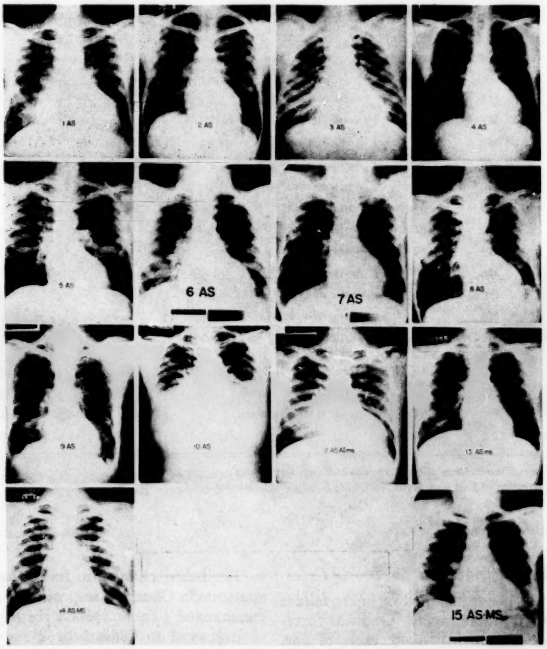

FIGURE 2. *Preoperative Six-Foot Posteroanterior Roentgenograms of the Chest.*

are shown in Figure 3. Systolic-pressure gradient across the valve decreased from 60 to 30 mm. of mercury, diastolic pressure in the left ventricle was slightly reduced, and a slight tendency to ventricular alternans cleared. Decreases in systolic aortic and gradient pressures in the left ventricle were 25, 16 and 50 per cent, respectively.

10 felt improved after operation and described a reduction in severity of symptoms. Fatigue and dyspnea remained the most severe symptoms after operation (Table 1). In our clinical opinion, based on changes in limitation of physical activity as well as symptomatology, significant improvement occurred in 8 of these 10 patients.

TABLE 1. *Clinical Information.*

CASE NO.	PATIENT	SEX	AGE	LESION	DURATION OF SYMPTOMS	PERIOD OF INABILITY TO WORK	DURATION OF FOLLOW-UP STUDY
			yr.		yr.		
1	M.M.	M	35	Aortic stenosis	1½	2 mo.	9 mo.
2	D.J.	M	38	Aortic stenosis	1½	2 mo.	9 mo.
3	J.O'F.	M	44	Aortic stenosis	12	1 yr.	9 mo.
4	H.C.	M	47	Aortic stenosis*	10	3 mo.	11 mo.
5	E.S.	M	58	Aortic stenosis*	10	5 yr.	4 mo.
6	B.C.	M	58	Aortic stenosis*	2	2 mo.	3 mo.
7	D.O'D.	M	62	Aortic stenosis*	4	10 mo.	4 mo.
8	S.B.	M	42	Aortic stenosis*	½	6 mo.	(Death in 2 wk.)
9	N.McC.	M	58	Aortic stenosis*	5	1 yr.	(Death in 2 mo.)
10	M.G.	F	58	Aortic stenosis*	8	2 yr.	(Death in 3 mo.)
11	E.A.	M	36	Aortic stenosis & insufficiency	5	1 yr.	1 mo.
12	T.C.	M	39	Aortic stenosis & insufficiency & mitral stenosis	5	8 mo.	6 mo.
13	C.W.	M	50	Aortic & mitral stenosis	3	0	6 mo.
14	H.W.	M	29	Aortic & mitral stenosis*	2	5 mo.	4 mo.
15	M.H.	F	53	Aortic & mitral stenosis	4	2 yr.	5 mo.
	Average†		47.1		4.9	12.1 mo.	6.4 mo.

*Associated murmur of aortic insufficiency without suspected clinical significance.
†Excludes cases 8-11 in duration of follow-up study, symptoms & functional classification.
‡Scale, 0-4.
§Denotes syncope.
¶New York Heart Association classification.

Postoperative Mortality

Three patients (20 per cent) died of heart failure two to twelve weeks postoperatively. One was forty-two, and the other 2 were fifty-eight years of age. Before operation the older patients had been seriously limited over a period of years by symptoms of left-ventricle failure; the younger patient had been disabled for a few months by syncope. Aortic insufficiency appeared postoperatively in only 1 of these patients (Case 9). All 3 had calcified valves and at least moderate enlargement of the left ventricle preoperatively (Fig. 2). Autopsy examination of 1 patient (Case 10) showed splitting of two commissures, resulting in a slit orifice approximately 2 by 25 mm., with heavily calcified and rigid valves that prevented adequate mobility.

Clinical Course in Survivors

Subjective criteria. Of the 12 surviving patients,

Regarding changes in functional capacity, of the 8 patients in Class 3, 4 improved to Class 2, and 4 were unchanged (Table 3). Of the 4 patients in Class 4, 3 improved to Class 1 or 2 status, and 1 was unchanged. Thus, 7 of the 12 showed improvement by this criterion.

Improvement by functional classification was further analyzed in relation to age (Table 4). Whereas the median age of 5 unimproved survivors was fifty-eight, that in 7 who improved was thirty-nine years. Restricted to 7 survivors with isolated aortic stenosis, the median age of 4 improved patients was forty-one, as opposed to fifty-eight years in 3 who were unimproved.

Of 4 patients who also had mitral commissurotomy at the same operation, 3 were improved, and 1 was unchanged. However, of 10 patients with isolated aortic stenosis, only 4 were improved, 3 remained unchanged, and 3 died. Significant aortic insufficiency

was present preoperatively in 2 patients. One (Case 11) failed to improve, and showed no change in aortic insufficiency. The other patient (Case 12), also with mitral stenosis, improved considerably.

Objective criteria. Objective criteria of improvement are the work record, need for medications and laboratory data. Only 1 patient (Case 13) had been operatively. Changes in fluoroscopic evidence of enlargement of the left ventricle were not impressive. There was some reduction in heart size in 2 patients, and an increase in 1; these changes were poorly correlated with other evidence of improvement.

In the 11 cases (including 2 deaths) in which direct recordings of peripheral arterial pressure were

TABLE 1 *(Concluded).*

CASE NO.	SEVERITY OF SYMPTOMS‡												FUNCTIONAL CLASSIFICATION¶	
	FATIGUE		DYSPNEA		PAROXYSMAL NOCTURNAL DYSPNEA		EDEMA		ANGINA		CEREBRAL			
	pre-operative	*post-operative*	*pre-operative*	*post-operative*	*pre-operative*	*post-operative*	*pre-operative*	*post-operative*	*pre-operative*	*post-operative*	*pre-operative*	*post-operative*	*pre-operative*	*post-operative*
1	4	0	4	0	3	0	3	0	0	0	1	0	IV	I
2	4	2	3	1	3	1	3	0	1	0	2	2	IV	II
3	2	1	2	0	2	0	2	0	0	0	0	0	III	II
4	2	1	2	0	2	0	2	0	0	0	0	0	III	II
5	4	2	3	2	2	1	1	0	2	1	0	0	III	III
6	0	0	3	2	3	0	2	0	3	3	0	0	III	III
7	3	3	4	4	2	2	0	0	0	0	0	0	III	III
8	0		0		0		0		0		4§		III	
9	2		4		2		2		2		3§		III	
10	4		4		3		3		3		0		IV	
11	4	4	2	3	2	3	0	0	2	2	0	0	III	III
12	3	0	3	1	1	0	1	0	4	0	0	0	IV	II
13	3	1	4	2	0	0	1	0	0	0	0	0	III	II
14	3	1	4	1	2	0	1	0	3	0	2§	0	III	II
15	4	4	4	1	0	0	3	0	0	1	3	0	IV	IV
	2.9	1.4	3.4	1.4	1.9	0.4	1.6		1.5	0.6	1.0	0.3	3.4	2.4

*Associated murmur of aortic insufficiency without suspected clinical significance.
†Excludes cases 8-11 in duration of follow-up study, symptoms & functional classification.
‡Scale, 0-4.
§Denotes syncope.
¶New York Heart Association classification.

able to work preoperatively and was limited to two or three hours a day in his own carpentry shop; postoperatively, he is working twice as long in the same trade. Five others are now working full time in nonstrenuous occupations (Cases 1, 2, 4, 11 and 12). Two additional patients are planning to resume work in the next few months (Cases 3 and 14). The remaining 5 patients are still unemployable by virtue of their symptomatology or, as in 1 patient (Case 5), a combination of age and lack of skills.

Although 4 patients no longer need either sodium restriction or diuretics, all have continued on digitalis preparations.

Before operation there were electrocardiographic findings interpreted as left-sided heart strain in 10 of the 12 survivors. The remaining 2, with associated mitral stenosis, showed a "balanced" tracing, or suggestions of combined heart strain. There were no changes in these electrocardiographic findings postmade before and after operation, there was no change in the average values of systolic (135 to 136) and diastolic (65 to 62) pressures. Significant increase in systolic pressure occurred in 3 out of 6 improved patients and in 1 of 5 unimproved patients. The average upstroke time for these patients was reduced from 0.19 to 0.17 second postoperatively. Of the 8 patients showing a decrease in upstroke time of 0.02 second or more, half were improved by other criteria, and 2 deaths occurred. Two patients, both of whom were considered improved, showed lengthening of the upstroke time of 0.03 second or more. The remaining patients had intermediate changes in upstroke time.

In 11 of the 12 survivors exercise data were available before and after operation* (Table 2). Whereas preoperatively there was only 1 physical-fitness-index score in the normal range (13-26), postoperatively 10

*Except for 2 patients (Cases 1 and 2), who were Class 4 before operation and too disabled to attempt the test.

patients had normal scores. Likewise, only 2 patients completed the exercise period of ten minutes preoperatively, whereas 9 did postoperatively. The same 9 patients also significantly increased their physical-fitness-index values by 6 units or more. Average values for endurance, heart rate in recovery and physical-fitness-index scores were also improved. In addition severity of symptoms during this standardized exercise test was reduced considerably. Thus, objective evidence of improvement was demonstrated in 9 of 12 survivors.

pretation difficult. Importance of selecting patients was indicated by the higher incidence of severe disability in persons under forty years of age. Results might vary with older patients who are more severely ill. Because of the brief follow-up period (averaging six and four-tenths months) only the early findings can be evaluated. Therefore, any deductions from these observations should be made in recognition of these limitations.

In contrast to the lack of operative mortality in this series, Bailey,[1] with the largest series presented to

TABLE 2. *Laboratory Information.*

Case No.	Electrocardiographic Findings	Valvular Calcification*	Cardiothoracic Ratio	Direct Arterial Pressure				Exercise Tolerance				Physical Fitness Index	
				Systolic Diastolic		Upstroke Time (seconds)		Endurance (minutes)		Recovery Heart Rate†			
				pre-operative	*post-operative*	*pre-operative*	*post-operative*	*pre-operative*	*post-operative*	*pre-operative*	*post-operative*	*pre-operative*	*post-operative*
1	Left-sided heart strain	2	0.67	—	120/70	—	0.22	—	10.0	—	271	—	21
2	Left-sided heart strain	0	0.51	124/72	124/50	0.20	0.20	—	10.0	—	305	—	17.1
3	Left-sided heart strain	0	0.53	128/90	164/86	0.18	0.23	10.0	10.0	264	251	12.1	20.7
4	Left-sided heart strain	3	0.56	155/62	152/72	0.14	0.09	3.0	10.0	475	334	2.6	20.1
5	Left-sided heart strain	3	0.50	128/60	104/50	0.18	0.14	6.8	10	265	259	14.5	20.4
6	Left-sided heart strain	0	0.59	136/56	180/84	0.23	0.20	6.5	4.5	351	366	5.6	3.0
7	Left-sided heart strain	0	0.50	104/46	104/46	0.24	0.15	7.0	3.5	192	216	12.7	13.5
8	Left-sided heart strain	2	0.50	—	—	—	—	—	—	—	—	—	—
9	Left-sided heart strain	4	0.52	144/79	110/40	0.22	0.16	—	—	—	—	—	—
10	Left-sided heart strain	3	0.73	154/72	138/64	0.19	0.16	1.5	—	287	—	1.0	—
11	Left-sided heart strain	?	?	—	—	—	—	2.0	—	207	—	4.1	—
12	Left-sided heart strain	0	0.60	160/60	130/47	0.16	0.19	10.0	10.0	261	258	11.8	17.8
13	Left-sided heart strain	0	0.47	106/64	136/70	0.19	0.16	3.0	10.0	369	321	2.8	16.2
14	"Balanced" tracing	0	0.49	126/56	(Damped)	0.17	0.16	3.0	10.0	295	258	6.0	19.7
15	"Balanced" tracing	0	0.62	144/64	158/68	0.16	0.19	6.0	10.0	246	239	9.1	19.7
Averages			0.56	135/65‡	136/62‡	0.188§	0.169§	6.1¶	8.7¶	302¶	278¶	8.6¶	16.8¶
									8.9		280‖		17.2‖

*Valvular calcification on fluoroscopy; 1, slight; 2-3, moderate; 4, marked.
†Total number of heart beats in 1st 3 minutes of recovery.
‡Includes 11 patients with both preoperative & postoperative determinations.
§Includes 12 patients with both preoperative & postoperative determinations.
¶Omits Cases 1, 2 & 8-11.
‖Omits Cases 8-11 only.

The 3 late postoperative deaths occurred in the group of 6 patients who had known valvular calcification. Yet substantial improvement in exercise tolerance occurred in the other 3 patients (Cases 1, 4 and 5). Among the 8 patients without demonstrable calcification, there were no deaths, and improvement occurred in exercise tolerance in all but 2 (Cases 6 and 7).

Discussion

There are several limitations in the evaluation of aortic commissurotomy from these observations. Both a small number of patients and significant mitral stenosis or aortic insufficiency in a few render inter-

date, reported an operative mortality of 28 per cent (68 patients) with the transventricular and 15 per cent (47 patients) with the transaortic approach. Our experience is similar to the early experience of Muller and Hyman,[2] who mentioned only 1 operative death in their initial series of 13 patients operated on by the transventricular approach. However, a mortality of 27 per cent was later reported by Muller[3] as his series enlarged to 37 patients. The operative mortality in other series of 17 to 35 patients has been similar to this (Johnson,[4] 24 per cent, Glover,[5] 32 per cent, and Brock,[6] 29 per cent). Absence of operative deaths in the present group of patients, as well as serious hemorrhage and arryth-

mia, is attributed chiefly to the small ventriculotomy needed with the modified dilator described above.

Dissatisfaction with the transventricular approach by others has been attributed to precipitation of ventricular fibrillation, hemorrhage from a large ventricular incision and disadvantages inherent in any blind approach. Thus, the transaortic approach is now recommended exclusively by some to allow direct palpation and finger fracture.[1] Such an approach, combined with hypothermia, allows direct vision and dissection and has been successfully done recently.[8] Our operative experience to date tends to invalidate these first two criticisms of the transventricular approach. Furthermore, there is some doubt in our minds whether finger fracture via the transaortic approach really offers an additional advantage. As determined by the pathology of the valve, the commissures capable of being split will do so regardless of approach and instrumentation. The fact that certain valves undoubtedly cannot be helped by any method presently available should stimulate future surgical thinking in the direction of valvular excision and prosthetic replacement.

Comparison of different subjective and objective criteria of improvement in survivors is shown in Table 5. There was no discrepancy in 10 of 12 cases regarding the patient's opinion of improvement and description of severity of symptoms. Our clinical opinion differed only by lack of significant improvement in 2 of these 10 patients. This was due to only partial reduction in severe complaints in 1 case and to continuation of limiting psychiatric factors in another. By functional classification a fifth patient was unimproved, since his activity restrictions remained about the same although the symptoms were decreased. Thus, these multiple subjective criteria indicated improvement in 58 to 83 per cent.

Nine patients, or 75 per cent, showed improvement in exercise tolerance as evaluated by performance on a treadmill. These were the same 8 patients who were improved in our clinical opinion, in addition to the patient whose limitations were mainly of psychiatric origin.* Improvement in other objective criteria, such as arterial pressure and upstroke time, were less consistent, whereas changes in the electrocardiogram and enlargement of the left ventricle were negligible within the period observed.

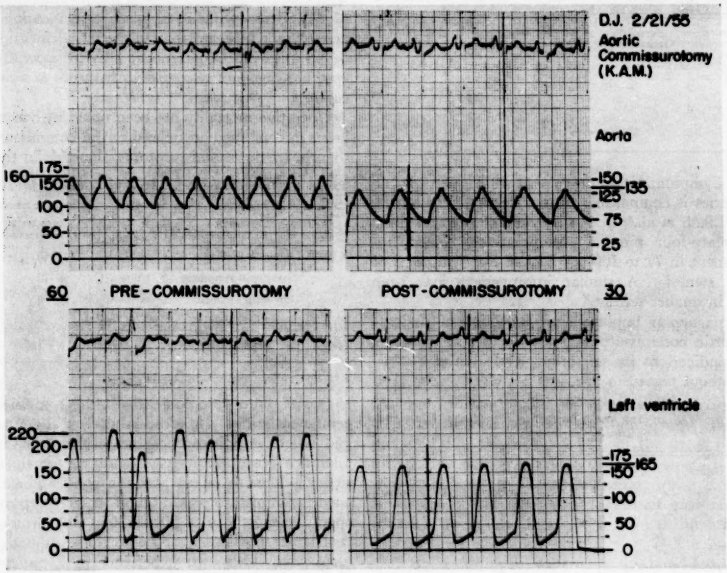

FIGURE 3. *Direct Pressures in Left Ventricle and Aorta before and after Commissurotomy.*

*This good correlation between treadmill performance and subjective indications of improvement is in contrast to similar studies in this laboratory in 31 patients evaluated an average of twenty-one months after mitral commissurotomy.[9] Although 29 patients (94 per cent) of the latter group considered themselves better, only 16 (55 per cent) had improvement in exercise tolerance on the treadmill. Not only was the correlation between objective and subjective criteria better in aortic commissurotomy, but also the percentage of patients with improvement in physical-fitness-index scores and average increases in endurance and physical fitness index were also more striking in aortic commissurotomy. These comparative findings, then, suggest that survivors of aortic commissurotomy may show greater increases in exercise tolerance and a better correlation of subjective and objective criteria of improvement than survivors of mitral commissurotomy.

Although effects of surgical therapy in valvular heart disease are best made by comparison with a similar, nonsurgically treated group, such a control series is lacking in the present report. The usual steadily progressive nature of symptomatic aortic stenosis, often with relatively abrupt deterioration, emphasized in other studies of the natural history of this disease,[10-13] suggests that the objective evidence of improvement noted in 75 per cent of survivors in this series is properly attributed to surgical intervention. Symptomatic improvement of 83 per cent in this series is comparable to that reported by others. Thus Likoff et al.,[14] in 44 survivors followed for three to twenty-four months postoperatively, noted improvement in 77 to 100 per cent of five symptoms of aortic stenosis. A similar improvement has been noted in smaller series.[4-6]

TABLE 3. *Changes in Functional Classification of Survivors.*

Before Operation			After Operation			
Class	No.		Class 1	2	3	4
3	8	→	0	4	4	0
4	4	→	1	2	0	1
	12	→	1	6	4	1

Of particular importance in selection of patients for aortic commissurotomy are factors constituting contraindications for operation. Duration of disability, without regard to age, was not clearly related to benefits observed in the present series. Severe disability is not a contraindication in that striking improvement was obtained in some Class 4 patients. In the series of Likoff et al.[14] operative mortality varied directly with functional classification. Paroxysmal nocturnal dyspnea, edema or orthopnea occurred preoperatively in all our survivors. Of greater importance is the failure to relieve such symptoms by intensive medical treatment. This is stated by Likoff et al.[14] to be an absolute contraindication to operation. Only 1 of our patients (Case 10) failed to show such improvement before operation, and she died twelve weeks postoperatively. The few cases of improvement and the higher mortality observed in patients over fifty-seven years of age indicate that advanced age is a relative contraindication to operation. This is in keeping with the observations of Likoff et al.[14] of a fourfold increase in operative mortality in pure aortic stenosis in patients over fifty years of age.

TABLE 4. *Median Age and Changes in Functional Classification of Survivors.*

Group	No. of Cases	Median Age in Improved Survivors	Median Age in Unimproved Survivors
		yr.	yr.
All patients	12	39	58
Patients with aortic stenosis only	7	41	58

In spite of adequate commissurotomy heavily calcified and rigid valve leaflets may fail to open at physiologic pressures, as demonstrated in postmortem studies by McMillan.[15] Extensive calcification may make commissurotomy impossible. Thus, the presence of valvular calcification on fluoroscopy might be expected to be an unfavorable sign. Our 3 late postoperative deaths were confined to patients with such recognized calcification. Yet 3 survivors with calcification also showed improvement, as did 6 of 8 patients without apparent calcification. It is accordingly believed that valvular calcification may be an unfavorable prognostic sign for operative success, but does not necessarily constitute a contraindication.

Operative mortality has been noted by others to be lower in combined aortic and mitral commissurotomy than in aortic commissurotomy alone.[2,7] In the present series there were no deaths in the 4 patients with combined lesions. In addition all 4 of these patients had objective evidence of improvement in exercise tolerance postoperatively. Significant aortic insufficiency is said to be an absolute contraindication to aortic commissurotomy. Likoff et al.[14] reported an operative mortality of 50 per cent due primarily to ventricular fibrillation or hemorrhage or both in 10 such cases. Our own experience in 2 patients has been equivocal. One failed to improve, but the other, who also had mitral stenosis treated, has shown marked improvement.

TABLE 5. *Improvement by Multiple Criteria in 12 Cases.*

Criterion	Cases with Improvement
Patient's opinion	10
Severity of symptoms	10
Physician's opinion	8
Functional class	9
Exercise test*	9

*Follow-up data available in only 11 cases.

Summary

Observations are presented from a short-term follow-up study of 15 patients who underwent transventricular aortic commissurotomy with a modified dilator.

There were no operative deaths, although 3 patients died within subsequent weeks.

The opinions of patient and doctor, as well as results of functional classification and exercise tolerance, were in close agreement, indicating improvement in about 75 per cent of survivors.

Impressive improvement after aortic commissurotomy was restricted to younger patients.

Factors germane to the selection and evaluation of patients are discussed.

Since this paper was submitted for publication, Case 11 was evaluated eleven months after operation. In contrast to the findings one month after operation, when there was no evidence of improvement, he was now improved by subjective criteria, functional classification and exercise tolerance.

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MEDICAL PROGRESS

PROCTOLOGY

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THE last report of this nature in the *Journal* appeared in the issues of August 19 and 24, 1954, from which point the present review carries on. It is not always easy to decide, in reading various articles, whether they represent "progress" or just another point of view on the same subjects, based on the writers' own ideas, experience and favorite methods that are bound to differ one from the other.

One would think, for example, that the facts of anatomy would have been settled beyond argument years ago by the many excellent anatomists of the world's medical schools. And yet contributions on this subject still appear and raise doubts about who is right.

Anatomy

Goligher, Leacock and Brossy,[1] by a dissection of the anal canal in 14 specimens removed by abdominoperineal resection, have made several points at variance with previously accepted anatomic findings of Milligan and Morgan. In brief, they are sure that the relatively superficial muscle band encountered in excision of a fissure, or in removal of internal hemorrhoids, is really the lower border of the internal sphincter, which has been dragged downward by traction, rather than the superficial or subcutaneous part of the external sphincter. They point out, also, that it lies in the same place, and fits in appearance the description of what Miles has called the "pecten band," division of which is an important part of an operation for fissure.

Since these authors acknowledge indebtedness to Milligan and Morgan "for much helpful advice and criticism," it may be assumed that the latter have been won over to this new concept, but in any case it is probable that all are agreed about the value of cutting this prominent bandlike structure, which is often seen standing out like a bowstring, quite inelastic, across the bed of the wound of fissure excision, and which is the chief obstacle to a normal dilatation of the anus during defecation.

In my own surgical experience this band has shown the whiteness and inelasticity of scar tissue rather than the redness and softness of muscle, but may well represent fibrosis of the lower border of the internal sphincter.

The book of Gorsch[2] on proctologic anatomy, which is probably the best, and perhaps the only, book on the anatomy of this area written by a surgeon doing proctologic work, is well worth reading.

Hemorrhoids

Jackman,[3] at the Mayo Clinic, has stated certain principles in the handling of hemorrhoidal thromboses that happen to coincide quite closely with my own ideas and practice in the management of these conditions. His ideas are as follows:

Simple localized external thrombosis, if present for more than four days, is usually left alone since the period of intense discomfort is about over. If

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present for less time it is excised, under local anesthesia and with removal of the overlying skin and all clots, without suture of the radial elliptical incision. Bleeding is controlled by pressure.

Ulcerated local thrombosis is treated by evacuation of the residual clot, if present, and control of bleeding by pressure.

Frequently recurring external thrombi are considered an indication for hemorrhoidectomy.

Thromboses during pregnancy, if small, are dealt with surgically as described above. If extensive, conservative measures are often used, such as hot or cold packs, witch-hazel compresses and codeine with aspirin, but hemorrhoidectomy is not contraindicated if the size and degree of pain are so great as to make it desirable to obtain immediate relief by surgery.

Prolapsed strangulated hemorrhoids are treated by immediate hemorrhoidectomy, as a rule, unless the mucosal part of the swelling can be reduced, leaving a relatively small amount of external involvement with edema that gives promise of subsidence. If there are extensive external thromboses all around the circumference it is better not to delay surgery.

Jackman points out the lack of value of ointments or suppositories either in hastening subsidence or in relieving the pain of thrombosed or prolapsed hemorrhoids. He also avoids the injection of oil anesthetic agents in these lesions because of the not infrequent complications of abscess and incontinence that may follow their use.

Turell,[4] in a recent editorial on hemorrhoids in general, sums up their treatment in a nutshell by saying that they can be "neglected, injected, or resected," placing 20 per cent of his own patients in the first category, 30 per cent in the second and 40 per cent in the third, reserving the remaining 10 per cent as borderline cases.

He favors an open, nontraumatizing excision operation, in all cases, immediate operation for strangulated internal hemorrhoids and avoidance of long-lasting anesthetic solutions, and does not approve of periodic digital examinations after operation, considering them unnecessary for a good result. Only with the last point do I disagree, but I admit that in many cases it is probably unnecessary. Periodic inspections until the patient thinks he is almost normal again are valuable in detecting occasional complications early and in the reassurance it gives the patient to be carefully watched until healed. Whether digital examination is performed at each visit may well be left to the surgeon's discretion based on his knowledge of the exact operative procedure.

Anal Infections

Nesselrod[5] believes that infection in the anal crypts and their glandular structures is the basis of the development not only of perianal abscess and fistula, about which there is no argument, but also of fissure and hemorrhoids. The concept of anal fissure as being an ulcer resulting from necrosis of the covering of a small underlying superficial infection is a reasonable one and may well be correct. But to attribute the development of hemorrhoids to the weakening of the vein walls as a result of infection in and around them is harder to prove. Nesselrod, however, has conducted microscopical studies (to be published later) in which the presence of the anal ducts and of round-cell infiltration can be seen in close proximity to the venous structures of the anal canal, not to mention the obvious cases with edema, swelling, thrombosis, phlebitis and so forth indicating gross infection.

Rosser[6] discusses the role of antibiotics in the treatment of anal infections, the resistance of certain bacterial strains to one or another drug, and their susceptibility to others, which points up the necessity of picking the right antibiotics for the particular patient as determined by sensitivity tests. Penicillin and streptomycin, in Rosser's experience, have not been very efficient when *Endamoeba coli* predominates whereas chloramphenicol gives promise of better results, but the former were efficient against the hemolytic streptococcus in 10 of 11 strains, as was chlortetracycline. He mentions bacitracin as being effective against the staphylococcus in 75 of 86 strains tested.

Rosser rightly emphasizes, also, that the use of these drugs is no substitute for early drainage of an abscess or for an adequate surgical attack upon a fistula, but puts in a plea against the indiscriminate incision of fistulas coincident with drainage of an acute abscess as favoring more frequent development of incontinence than would occur if the fistula were dealt with at a later date. Prolonged packing of fistula incisions has been recognized as another factor favoring incontinence.

Perianal Sinuses

Hill,[7] at the Mayo Clinic, discusses perianal abscess and sinuses in connection with which no rectal origin, or internal opening, could be found. This group embraced 14 per cent of the patients operated on at the Mayo Clinic in the Section of Proctology. The origin of such lesions may be in a sebaceous or sweat gland, along a hair follicle, in a pilonidal or presacral cyst, osteomyelitis of the coccyx or other pelvic bones, Bartholin's glands, the male urethra, trauma or a foreign body introduced through the skin. Hill gives one case report in which a sinus near the rectum was found by injection of an opaque solution to connect with the sigmoid, subsequent resection showing it to have had origin in a ruptured diverticulum.

With the much greater frequency of sinuses originating in an internal fistulous opening in the rectum it is obvious that every effort must first be made to exclude this mode of origin, the treatment of which is, of course, clear cut.

Stricture and Incontinence

In discussing *strictures of the rectum* Fansler and Neumeister[8] use the term "annular" to describe strictures of 2 cm. or less in length, and the term "tubular" to describe those over 2 cm. in length. For the former type gentle dilatation, prolonged over a considerable period, is advocated, but in some cases multiple radial incisions in addition are necessary. For the tubular strictures, and some of the annular type, resection with anastomosis or a "pull-through" procedure is employed, with an occasional abdominal colostomy if necessary. The importance of waiting until active infection has subsided is stressed.

The *incontinence* that may follow division of the sphincters in operations for fistula and the factors that produce it are emphasized by a summary of the conditions necessary to continence: capacity of the sigmoid and rectum to store feces and gas; angulation of the anal canal in relation to the rectum; anatomy of the musculature of the lower rectum and anal canal; slight recurrent involuntary contractions of the sphincters; and voluntary contractions of sphincters.

Repair of anterior or lateral defects resulting in incontinence from division of the sphincter are handled as follows: the muscle ends are located and dissected free of all surrounding scar tissue except a small amount left on the muscle ends to give better support for the sutures used in approximating these ends; such a dissection may have to be carried halfway around the anal outlet to free the muscle adequately and to permit suture without tension. Chromic catgut No. 00 or No. 000 is used, and the skin left open or lightly closed. Nonabsorbable sutures are considered to have no real advantage and are more likely to produce persistent sinuses.

When the defect is posterior there is usually a destruction of the anorectal angle and injury to the rectal reservoir and the repair includes reconstruction of this angulation by suture of the freed muscles, which are approached by an incision through the old scar to a point beyond its upper end. This incision goes into the rectum for a short distance, and the mucosa is sutured again before closure of the muscles. (One wonders why it is necessary to extend this incision inside at all, running the risk of another fistula through the sutured mucosa.)

Preoperative preparation includes the use of succinylsulfathiazole, 3 gm. four times a day for a week, and neomycin, 1 gm. four times a day for forty-eight hours, with enemas during the night before and on the morning of operation.

Pickrell and his associates,[9] from Duke University, describe an operation for anal incontinence that they have used in 30 patients, from three to seventy-two years of age, with almost uniform success. The gracilis muscle, most superficial of those of the inner thigh, is freed through an upper and lower incision on the thigh, and through a third incision over its tendinous insertion below the medial condyle of the tibia, where it is dissected free of the tibia, including some periosteum.

The muscle is then mobilized upward until its nerve and blood supply can be seen entering it on the lateral aspect, indicating adequate mobilization. Then, with the patient in exaggerated lithotomy position and with the use of two incisions 1.5 cm. from the anus, at 12 and 6 o'clock, a subcutaneous tunnel is constructed around the anal canal, preserving the anterior and posterior raphes for use as pulleys. Another tunnel is constructed from the upper thigh incision to the 12 o'clock perianal incision and the free end of the gracilis brought through this tunnel to the 12 o'clock incision, continued around the anus behind the posterior raphe and back around the anterior pulley again, if there is room enough, or otherwise behind the gracilis body to be then sutured on the opposite side from the muscle origin, to the inguinal ligament, adductor muscles or ischial tuberosity. The anus must be snugly closed by this maneuver, and all incisions are closed without drainage. Only one gracilis is used. A careful reading of this article will clarify details in technic briefly sketched above.

Previous procedures of this type have utilized free fascial strips, as in the Stone modifications of the Wreden operation, but the authors believe their procedure to be an original principle.

Banov[10] reports from South Carolina a five-year experience in the treatment of rectal strictures due to lymphogranuloma venereum by the use of broad-spectrum antibiotics, with improvement of varying degree in all patients. The drugs used were as follows: chlortetracycline in 12, chloramphenicol in 8, oxytetracycline in 8, erythromycin in 3 and tetracycline in 3 patients, all 34 being Negroes.

All cases were diagnosed by either a positive Frei test or a positive complement-fixation test. Improvement consisted in reduction of the inflammatory component of the strictures, with reduction or elimination of bleeding, purulent discharge, edema around the stricture and pain. Improvement was usually noted in three to five days. The first three drugs were effective in doses of 750 to 1000 mg. daily for twelve to twenty-five days. Erythromycin was given in a dosage of 1600 mg. daily for a similar period. Tetracycline had not been used long enough to be evaluated.

Antibiotics and Intestinal Antisepsis

The effect of certain antibiotics in the production of diarrhea, pruritus ani, proctitis, perianal edema and dermatitis has been encountered with increasing frequency since the introduction of these drugs.

Manheim and Alexander,[11] in a report of 300 cases, have called further attention to these now well recognized anorectal complications that follow the use of chlortetracycline, oxytetracycline and chloramphenicol in the treatment of a wide variety of illnesses. These authors, in 1951, reported 100 cases of similar nature.

In the present series the drugs had been given, in two thirds of the cases, for usually self limited ailments such as common colds, sore throats, "virus infections," and "flu," in which the drugs cannot be considered specific remedies. Chlortetracycline was the offender in 171 cases, oxytetracycline in 95, chloramphenicol in 13, and combinations in the remaining 21.

Symptoms started one or two weeks after ingestion, diarrhea often being the first symptom, as in 40 per cent of this series.

Sigmoidoscopic examinations revealed a normal mucosa in the majority of cases but an acute ulcerative colitis in 5 and an acute ulcerative proctitis in 14. Abscesses, fistulas or ulcers necessitated surgery in 15 patients.

Pruritus, the commonest single symptom (207 cases), responded promptly to use of fungicidal powders and oral intake of buttermilk, yogurt or acidophilus milk, but recurrences developed in over two thirds of the patients without further ingestion of the drugs, and half were having symptoms after two years, as determined by questionnaires. In two thirds of the entire series no rectal symptoms had been present before the use of these drugs, and in 81 of 100 patients who had had some rectal symptoms previously, the present symptoms were entirely different. Also, the onset and severity of symptoms had no relation to the amount of the drug used.

Poth,[12] from the surgical research laboratory of the University of Texas Medical Department, discusses the requirements for efficient intestinal antisepsis and the dangers inherent in the possible overgrowth of certain bacteria when others that normally inhibit them have been killed off by the drugs.

As a result of the use of chlortetracycline, oxytetracycline and chloramphenicol, in some cases, an overgrowth of *Micrococcus pyogenes* has produced the so-called choleriformic syndrome with nausea, vomiting, bloody diarrhea, high fever and death in four or five days. Erythromycin, at first efficacious against the staphylococcus, has now been found to be of no use against certain strains.

Poth cites the use of neomycin as a preoperative agent in 750 patients without a single case of this serious complication. In combination with phthalylsulfathiazole neomycin has given the best results.

Antibiotics in Nonobstructed Patients

Poth prepares a nonobstructed patient for colonic surgery in twenty hours by a schedule starting the afternoon of the day before surgery as follows: at 1 p.m. 60 ml. of castor oil, 1.0 gm. of neomycin, and 1.5 gm. of phthalylsulfathiazole; and at 2, 3, 4 and 8 p.m. and at 12 midnight and 4 and 8 a.m. the same dosage of neomycin and phthalylsulfathiazole is repeated, and surgery scheduled an hour later — at 9 a.m.

Antibiotics in Partially Obstructed Patients

No purgative is used, and the drugs mentioned above are given at four-hour intervals over a period of three days as a rule, combined with gastric suction.

Antibiotics in Emergency Cases

When the abdomen is opened, in cases of perforation of the bowel, acute obstruction and so forth, the fluid is aspirated, and 200 to 300 ml. of a 1 per cent neomycin solution is poured into the peritoneal cavity. After closure of a perforation, or resection if indicated, another 100 ml. is placed in the peritoneal cavity before closure of the abdomen.

In addition to this, when resection is to be done, clamps are applied to the bowel at the points selected for resection, and then 1 per cent neomycin solution is flooded through a needle puncture above and below the clamps into the lumen of the healthy bowel, the mesentery prepared for resection, and the bowel reclamped behind the other clamps, which are then removed, the crushed ends that have not been in contact with the neomycin within the bowel are excised, and open anastomosis is performed after removal of the second set of clamps.

These procedures with 52 patients in the past four years have resulted in no complications of suture lines, no persistent peritonitis and presumably no deaths, though this is not specifically mentioned. The rapid action of these two drugs in combination makes them highly desirable until such time as immunity to their action may be built up by some bacterial strains.

Pseudomembranous Ulcerative Colitis

Childs and Beatty[13] report 2 cases of fatal pseudomembranous enteritis in children aged one month and four days. In the first patient the disease developed sixteen days after resection of the sigmoid and six days after discharge from the hospital. There had been three days of preoperative preparation with 50 mg. of chlortetracycline every four hours and 0.5 gm. of succinylsulfathiazole three times a day, and postoperative use of Dicrysticin, 1 ampoule twice a day for nine days. Death occurring twenty-four hours after onset, an autopsy revealed a clean peritoneal cavity, pseudomembranous colitis and a post-mortem blood culture of hemolytic *Staphylococcus aureus*. Culture from the intestine showed pseudomonas, and *Escherichia coli* was found in tracheal culture.

The second child had no antibiotic therapy, but vomiting and abdominal distention developed, for which he was admitted to the hospital, and died after seven days. Autopsy revealed pseudomembranous ileocolitis, and bowel cultures showed a few enterococci, numerous colonies of *Proteus vulgaris* and a few of *Esch. coli*.

These authors emphasize the fact that fatal pseudomembranous enterocolitis is not a new entity, having been first reported in association with surgery by Finney in 1893. Also, since it is so rare, there does not seem to be reason to abandon the use of antibiotics, but efforts should be made to protect the patient against staphylococcal infection by culture of the bowel ends in an open anastomosis, and by culture of postoperative stools. If staphylococci are found, antibiotics should not be used or else an effort should be made to select the one to which the staphylococci are sensitive.

Jonassen, Fierst and Cincotti[14] encountered 2 patients with this disease, 1 of whom died nine days after gastrectomy whereas the second recovered after onset of shock. This second case is reported in detail, treatment consisting of restoration of blood pressure to normal by use of nor-epinephrine, restoration of fluid and electrolyte losses, discontinuance of broad-spectrum antibiotics and use of erythromycin and chloramphenicol, repeated whole-blood transfusions and human serum albumin, with ACTH later to improve appetite.

Anorectal Sepsis in Leukemia

Blank,[15] of Toledo, presents 5 cases of leukemia in which anorectal complications occurred. Such manifestations, though not common, have been reported by several other writers.

Of Blank's 5 patients 2 were children, three and a half and two years of age, with acute aleukemic lymphatic leukemia in whom perianal thrombosis developed, progressing to ulceration and abscess at or within the anal canal and lower rectum. The other patients were adults, of whom 1 had myelogenous leukemia and 2 had chronic lymphatic leukemia. Only in the two-year-old child did partial healing occur before death.

Presence of the ulcerating anorectal lesion led to the diagnosis of leukemia in 1 patient, as in a previous case report by Walsh and Stickley.

Conservative symptomatic treatment, rather than surgery, is indicated in these patients, in whom the lesions develop only when they are very ill and whose disease will shortly be fatal, with or without surgery.

Pedicle Grafts

There has been some interest in the past several years in the possibility of reconstruction of a badly scarred anal canal by the use of skin grafting, particularly the sliding or rotating pedicle graft. Fitzsimmons[16] describes 6 patients in whom he has rotated a pedicle from the buttock (in 1 case bilaterally) to be sutured to the rectal mucosa after excision of the scar that it was to replace. By the use of antibiotics before and after surgery he was able to obtain a "successful" result in all 5 cases, providing elasticity to the anal canal and, in combination with muscle suture, control in 2 patients whose chief complaint was incontinence.

Fitzsimmons does not mention which antibiotics he used, or the details of their use, but undoubtedly the healing of his grafts in this unclean area was due in no small measure to the effect of these drugs in reducing infection, as well as to careful technic, which was equally important. It would be too much to assume that there was not some slight stitch infection, but evidently it was so minor as not to interfere with a good functional result. That it is possible to obtain good results by grafts in this area opens up all sorts of possibilities in the reconstruction of anal canals formerly considered to have been irreparably damaged.

Idiopathic Colitis

There has been much speculation over the years about whether diffuse ulcerative colitis, segmental colitis, regional enteritis and regional enterocolitis are separate entities or merely diverse manifestations of the same disease. In none of them is the cause known, and yet all have points of resemblance and all are chronic inflammatory processes of unknown origin.

Manning, Warren and Adi[17] have selected 34 cases of *segmental colitis* from a group of 858 patients at Massachusetts General Hospital and West Roxbury Veterans Administration Hospital, between 1935 and 1952, who had one or the other of the syndromes mentioned above. Of these 34 cases the ileum was also involved in twenty-five, but the extent of ileal involvement was not over a few inches of terminal ileum and this was considered to be definitely secondary to the colonic lesion.

All 34 patients were operated upon, an anastomosis being performed with or without resection. In 19 patients relief of symptoms was obtained for an average of four and six-tenths years. This group of 19 included 15 of the 24 patients whose colons were resected and 4 of the 10 patients whose diseased colons were not resected. Anastomosis alone failed in 15 patients to produce a satisfactory result.

Thorlakson[18] has analyzed 182 consecutive colectomies for *ulcerative colitis* performed at St. Mark's Hospital, London, between 1949 and 1955 inclusive and found 12 cancers in the group — a 6.6 per cent incidence. Reports in the literature have shown a variation of 1 to 11 per cent, depending in part on the basis of calculations. As in a previous series from St. Mark's Hospital reported by Counsell and Dukes the carcinomas tended to develop during the quiescent stages of the disease.

The duration of colitis in Thorlakson's cases averaged seventeen years before cancer developed, and the average age of the patient at the time of diagnosis was fifty, varying from thirty to seventy-three

years. This average age at onset is ten to fifteen years earlier than in the general population.

There were 23 primary cancers in the 12 patients, 1 in the cecum, 4 in the transverse colon, and 18 in the descending colon, of which 14 were in the rectum or sigmoid.

The grade of malignancy was average or low in 18 of the 23 tumors, and there were no metastases in 7 of the 18.

Dennis and Karlson[19] present some conclusions based on a follow-up study of 267 patients with ulcerative colitis seen in Minneapolis hospitals from 1934 to 1951, of whom 61 per cent had fairly early elective surgery and 39 per cent had either no surgery or late operations of a more or less emergency nature. In the former group 80 per cent of those followed were alive in 1951, and 90 per cent of these were well. In the unoperated group only 29 per cent were alive, and about a fourth of these were free of symptoms. The incidence of cancer was 10 per cent in the whole series, whereas in patients who had their colitis for ten years or more this figure rose to 30 per cent.

Wheelock and Warren,[20] reviewing 713 cases at the Massachusetts General Hospital from 1915 through 1949, of which 483 were seen before 1943, were able to trace 343 patients for ten years or until death. Of these, 155 were living and 188 had died, 153 of these from their disease.

Before 1930 there was a 50 per cent mortality in all operations for ulcerative colitis. Ileostomy mortality has now dropped from 26.8 per cent in 1930-1939 to 12.5 per cent in 1940-1949 and 7.7 per cent in the 1950-1953 period.

Cancer developed in 28 of 319 patients (8.8 per cent) who had had their disease for ten years or more without colectomy and in 31 of the entire group. Of the 31 only 7 are alive, 2 for over five years.

In no case has the ileum proximal to an ileostomy developed ileitis.

Surgery was eventually resorted to in 48 per cent of the 483 patients.

It is now believed that with the disease still active after three years of medical treatment surgery should be advised.

Raven,[21] of London, describes a technic of one-stage colectomy for severe ulcerative colitis, with side-to-side anastomosis of the ileum to the anterolateral wall of the rectum at a point on the lower third of the rectum, after removal of the upper two thirds with the remainder of the colon. The open end of the rectal stump and the end of the ileum have been closed by a double row of sutures before the anastomosis. A rubber drainage tube is inserted through a lateral stab wound down to the vicinity of the anastomosis and removed after twelve days.

Reports of 4 patients, all of whom had rectal involvement, are given, and emphasis is laid on the fact that this is an operation for use in a small number of carefully selected cases. It has the advantage of immediate removal of most of the patient's disease and avoidance of an abdominal ileostomy. The fact that the anastomosis was carried out between normal ileum and a rectal stump with some degree of inflammatory disease apparently did not prove to be a serious problem.

Raven's statement that his procedure is for use only in a few selected cases deserves particular emphasis because there are many very sick patients in whom the risk of doing a one-stage colectomy is too great to justify its use, especially when ileostomy is combined with complete colectomy and abdominoperineal resection of the rectum as a single procedure. In the United States there is an increasing trend toward the latter operation in favorable cases.

(To be concluded)

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MEDICAL INTELLIGENCE

THALASSEMIA IN A FAMILY OF PURE GERMAN EXTRACTION*

JOHN E. MIDDLEBROOK, M.D.†

IOWA CITY, IOWA

THALASSEMIA, or Cooley's anemia, first clearly described by Cooley[1] in 1925, is a hereditary disease. Anemia results from the inability to utilize an adequate amount of the iron usually present in elevated levels in the serum. Although the disease is classically restricted to the Mediterranean races, sporadic cases have been reported in persons of many nationalities.[2] This report concerns an Iowa family of pure German extraction that was found to carry the trait for thalassemia in at least three generations. The rarity of thalassemia in families of German extraction[3] was considered to warrant a report of this study.

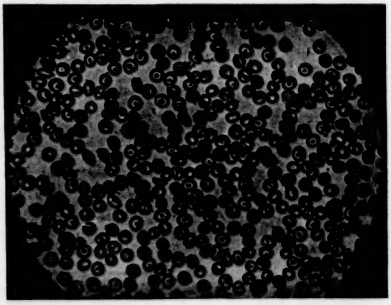

FIGURE 1. *Peripheral Blood Smear of Patient W.H.*

CASE REPORT

W. H., a 31-year-old carpenter, was first seen in August, 1954. He complained of an intermittent acute migratory arthritis of 7 years' duration. Abnormal physical findings on admission were limited to acute arthritis of 1 finger. The spleen was not palpable.

The family history revealed that a sister, 32 years of age, had been anemic since 1947 and that the patient's father had had recurrent arthritis for many years.

Examination of the blood showed a hemoglobin of 10.8 gm. per 100 ml., a red-cell count of 5,420,000, a hematocrit of 38 per cent and reticulocyte count of 1.5 per cent; the white-cell count was 11,100, with a normal differential smear. The cell indexes were as follows: mean corpuscular hemoglobin concentration, 32 per cent; mean corpuscular volume, 76 cubic microns; and mean corpuscular hemoglobin, 23 micromicrograms. The peripheral blood smear revealed many target cells, marked poikilocytosis and anisocytosis (Fig. 1). The uric acid was 8.5 mg. per 100 ml. A diagnosis of gouty arthritis was made. Treatment with probenecid (Benemid) and colchicine was followed by a complete remission of the arthritis. Maintenance doses of these drugs were continued, and the patient was discharged.

He was next seen in March, 1955, with complaints of continued vague weakness. Physical examination was negative. The hemoglobin was 10.3 gm. per 100 ml., and the peripheral blood picture was unchanged. X-ray films of the upper and lower gastrointestinal tract were normal. Stools were negative for occult blood. The total bilirubin was 0.8 mg. per 100 ml. of serum; fecal urobilinogen was 906

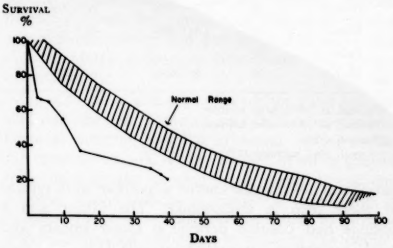

FIGURE 2. *Erythrocyte Survival, by Radioactive Chromium Technic, of Patient W.H.*

Ehrlich units in 24 hours, and a bone-marrow biopsy revealed only erythroid hyperplasia. Intravenous administration of 900 mg. of iron had no effect on either the symptoms or the peripheral blood picture, and the patient was again discharged.

In June he was admitted to the hospital for the 3d time with the complaint of weakness. Physical examination was again negative. The blood hemoglobin was 10.0 gm. per 100 ml., and the hematocrit 39 per cent. The serum iron level was 137 microgm. per 100 ml., a slightly elevated level, and a 2-hour plasma-iron-turnover study was normal. The peripheral blood smear again demonstrated abnormal cells. The red-cell fragility in hypotonic saline solution was decreased, with complete hemolysis at 0.12 per cent saline solution. The survival of the patient's red cells, when autotransfused, after tagging with Cr^{51}, was shortened to 65 days (Fig. 2). Additional studies revealed that the fetal hemoglobin was 3.1 per cent as determined by the alkaline-denaturation method. Filter-paper electrophoresis of the hemoglobin failed to reveal any abnormal hemoglobins.‡

A diagnosis of thalassemia was made, probenecid and colchicine were stopped, and cortisone, 200 mg. a day, was given for 51 days. There was neither symptomatic nor laboratory improvement with this therapy. With the exception of maintenance doses of colchicine and aspirin for the gout, there has been no therapy since.

The patient was last seen in May, 1956. The hemoglobin was 11.9 gm., and the other laboratory studies were unchanged. He was exhausted after working for only 4 hours a day as a bartender.

FAMILY STUDIES

The family was studied after the diagnosis of

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‡Low concentrations of fetal hemoglobin cannot be differentiated from normal Type A hemoglobin by filter-paper electrophoresis.

thalassemia was established in the patient. All members of the family were seen and examined. All were found to be normal with the exception of the father, who had far-advanced, generalized arthritis. None of the family had palpable spleens. The composite laboratory results are presented in Table 1. The

The patient's sister was the only other member of the family who was not symptomatically well. She first became aware of an anemia in 1947 at the age of twenty-four years. She was then in her fifth month of pregnancy, when weakness and dizziness became troublesome. She received iron and liver injections,

TABLE 1. *Blood Findings in Members of the Family.*

Member of Family	Age	Red-Cell Fragility		Hemoglobin	Red-Cell Count	Hematocrit	Fetal Hemoglobin‡	Serum Iron§	Peripheral Blood Smear
		Initial Hemolysis*	Complete Hemolysis†						
	yr.			*gm./100 ml.*	*x10⁶*	%	%	*microgm./ 100 ml.*	
Patient	31	At 0.42%	At 0.12%	10.8	5.42	37	3.1	137	+
Sister	32	At 0.42%	At 0.14%	9.6	5.29	34	3.5	157	+
Brother	24	At 0.40%	At 0.08%	11.5	6.15	43	4.7	107	+
Brother	19	At 0.44%	At 0.12%	11.5	5.69	41	4.9	116	+
Father	60			12.6	6.83	43	1.1		+
Mother	54	At 0.46%	At 0.28%	13.8	4.43	44	0.6	97	–

*Normal, at 0.44% saline solution.
†Normal, at 0.30% saline solution.
‡Normal, <1%.
§Normal, 104.7 microgm./100 ml.

peripheral blood smears noted as positive were typical of those seen in thalassemia. The father and 4 siblings had positive peripheral blood smears and mild hypochromic microcytic anemia (Fig. 3). Two members of the family had the compensatory polycythemia frequently seen in mild cases of thalassemia. The 4 siblings also had red cells abnormally resistant to hemolysis by hypotonic saline solution, whereas the mother's red cells hemolyzed completely at normal dilutions. Three of the siblings had slightly elevated serum iron levels (frequently seen in thalassemia[4]). The father's serum uric acid was 8.0 mg. per 100 ml. Electrophoresis of the hemoglobins of all members of the family revealed only hemoglobin of the adult type.*

Fetal hemoglobin determinations were performed by the alkaline-denaturation method of Singer, Chernoff and Singer.[5] For comparison the test was carried out in 53 normal subjects with a range of 0.0 to 1.8 per cent and an average of 0.73 per cent alkaline-resistant hemoglobin.

It was concluded, on the basis of these findings, that the gene for thalassemia was carried by the father and had been transmitted to all 4 siblings.

In addition to these studies peripheral blood smears were obtained from the 5 children of the patient's sister. Two of these children had the classic changes of thalassemia whereas the other 3 were normal. Unfortunately, these children were not available for physical examination or further laboratory procedures. Therefore, a diagnosis of thalassemia can only be assumed in them.

*Low concentrations of fetal hemoglobin cannot be differentiated from normal Type A hemoglobin by electrophoresis.

with no effect on either her symptoms or the anemia. Since that time she has continued to notice weakness and has been the subject of repeated courses of antianemic preparations, without noticeable improvement.

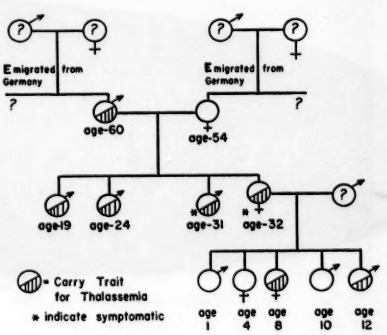

FIGURE 3. *Family Tree, Showing Affected Members in Three Generations.*

DISCUSSION

Although the family was thoroughly investigated and found to be of pure German extraction, the possibility of a mixture with Mediterranean blood at some time in the past cannot be ruled out. This mixing of blood many generations back may well be the mechanism of the occurrence of the disorder in a non-Mediterranean race.

The combination of gouty arthritis and thalassemia in both the father and the patient may well be coincidence. However, it is statistically unusual, and the possibility of a genetic relation between the two is raised.

Summary and Conclusions

A family of pure German extraction carrying the trait for thalassemia in three generations is described. This disease is rare in non-Mediterranean races.

I am indebted to Dr. Paul Hagen, Minneapolis, Minnesota, for his assistance in the determination of fetal hemoglobins.

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BY THE LONDON POST

National Hospital Day — Hunter House — A Heifer Calf

John Lister, M.D.

London, England

IT is obvious that there can be no regrets for the days when hospitals had to rely on charity for their maintenance. On the other hand National Hospital Day provided an opportunity for reminding the public of the service rendered by the old voluntary hospitals. It was an annual treat to see the nurses in the streets of London and elsewhere, each persuasively asking the busy city men to buy a flag for her hospital. The students, too, were glad to be granted a day's vacation to accompany a nurse on such an expedition, and it was almost a matter of competition between hospitals concerning which would collect the largest sum. St. Bartholomew's, to the north of the Thames, and Guy's Hospital to the south, were old sparring partners in this contest, as in many others.

With the advent of the National Health Service the organized collection of funds for the hospital service obviously ceased, and at first it was hard to see where there would be any place for voluntary effort. As the Service has developed it has become clear that the voluntary spirit was probably the intangible factor that gave a hospital its soul, and in recent years there has been a marked revival of voluntary work in association with the hospitals.

In particular the work of the King Edward's Hospital Fund for London is interesting. Instead of fading away with the coming of the National Health Service, the work of this fund, which relies entirely on voluntary contributions, has greatly increased in scope, and has helped hospitals to provide the kind of amenities that officialdom would never sanction from Treasury sources. Many of the old type of institutional hospitals have had their grim features greatly improved as the result of grants from this fund, and last year £250,000 was set aside to be spent over a three-year period in a number of mental hospitals. At one such hospital, it has been possible to plan a social center, with shops, a hairdresser, a bank and a library, for the patients, staff and visitors. Another project has been the purchase of a house to serve as a community center and day hospital to work with the psychiatric outpatient department of a general hospital.

In addition to this type of work the fund has carried out research into such problems as methods of hospital catering, and has arranged special courses for catering officers. Other courses in other subjects have enabled the nursing staff, medical staff and hospital administrators to discuss a wide range of hospital problems. Such courses seem to promise greatly enhanced co-operation between the doctors, nurses and administrators, and between one hospital and another, in making the adjustments needed today.

In the report issued earlier this year by the Guillebaud Committee, which inquired into the whole question of the cost of the National Health Service, it was stated that in hospitals there is still a large place for voluntary service and scope for more. Besides encouraging the work of such an organization as the King's Fund the committee called for local voluntary effort in the form of service. This has been forthcoming in an ever-increasing number of hospitals being helped by Leagues of Friends. Former patients, their relatives and many other interested people have formed themselves into groups to offer many kinds of voluntary service to the hospitals. Open days have been organized, and patients helped in cases of special need, and many amenities both for patients and for the staff are being provided by these efforts to ensure that although the hospital may be nationalized, it shall still have a soul.

* * *

Like so many Scots the Hunter brothers emigrated from their home in pursuit of their careers. Both William and John were born on a farm at Long Calderwood, 7 miles from Glasgow. William began his medical practice in Lanarkshire in partnership with William Cullen, who later became professor of medicine in Glasgow and was the first to deliver

lectures in the vernacular instead of in Latin. While Hunter and Cullen were in partnership they adopted the enlightened practice of releasing each other alternatively for further study of medicine. After a short time, however, William felt the urge to travel south to London, where he founded his school of anatomy, which was the center of anatomic learning in London for many years.

His brother John, who was the youngest of the family of eleven, later set out on horseback from the Long Calderwood farm to ride to London. He apparently reached his destination in a fortnight, and set about learning anatomy in his brother's school.

The subsequent careers of these two men are well known though that of John in a sense eclipsed his brother's, with whom he had an unfortunate quarrel in later life. Both men were remarkable collectors. John bequeathed his collection of specimens to the Royal College of Surgeons in London (though the original Hunterian Museum was badly damaged in the war it has since been beautifully restored). William, in turn, bequeathed to Glasgow University the Hunterian Museum of manuscripts, paintings, coins, anatomic preparations and zoologic and geologic specimens.

Now the opportunity has come to acquire and preserve the old farmhouse at Long Calderwood, Lanarkshire. The house, which is a typical Scots farmhouse, with white rough cast walls, is still occupied, and the land still farmed. Restoration of the fabric has become urgent, and to proceed with this work, a Hunter House memorial fund has been opened by the Royal College of Physicians and Surgeons of Glasgow. The sponsors hope to be able to create an endowment fund to preserve this memorial as a museum and a place of pilgrimage and perhaps later as a center for research.

* * *

One of the things that must keep the practicing physician alert is the fact that no two consultations are ever alike. It is so often said that things are not what they were that it is refreshing when a practitioner, when taking a colleague out in consultation, characterizes the patient as a real character and one of the old school. Such a piece of good fortune recently came my way.

The patient, inevitably of Irish extraction, had been married to an Army colonel, who had died, leaving her rather impoverished. To make ends meet she had taken a rambling old house and kept a small number of animals. We examined the patient in her sitting room. The first would-be intruder was a gander, which peered through the window. "Don't frighten him," said the patient, "he's my favourite gander!" Just as we were nearing the end of the consultation there was a knock at the door, quickly followed by the figure of a cowman. His message, in a broad country accent, was brief and to the point: "A heifer calf, madam," he said and disappeared. The doctor with whom I was consulting turned to the patient and said "Congratulations. I hope that was what you wanted."

She was apparently delighted, and her own symptoms seemed to have disappeared in the joy of this veterinary event. The doctor assured me that this incident was typical of her household and that he was sure her trouble must have been psychosomatic and related to the anxiety of her cow's confinement.

CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 42431

PRESENTATION OF CASE

An eighty-year-old widow entered the hospital because of abdominal pain.

Six weeks previously she had an attack of moderately severe epigastric pain. Subsequently, she remained well until three or four weeks before admission, when she noted the gradual onset of anorexia, early fullness after meals and episodes of "grinding," colicky pain in the right side of the abdomen. The pain, which was high at first, subsequently occurred lower in the abdomen and nearly always at night, causing her to awaken. There was one episode of spontaneous vomiting that was associated with the abdominal pain.

The patient had had pernicious anemia for fourteen years that was well controlled with liver injections. She had also taken iron orally.

Physical examination revealed a well nourished, elderly woman in no distress. Examination of the lungs was negative. The left border of cardiac dullness was at the mid-clavicular line. The cardiac sounds were diminished, and frequent extrasystoles were noted. Examination of the abdomen showed tenderness throughout both upper quadrants. The liver edge, which was irregular and tender, was felt 3 fingerbreadths below the right costal margin. The spleen was palpable 1 fingerbreadth below the left costal margin. Peristalsis was normal.

The temperature was 100°F., the pulse 95, and the respirations 16. The blood pressure was 135 systolic, 75 diastolic.

The urine was normal. Examination of the blood revealed a hemoglobin of 14.4 gm. per 100 ml. and a white-cell count of 6000. The nonprotein nitrogen was 14 mg., the total protein 6.9 gm., the albumin 4.3 gm., the globulin 2.6 gm., the bilirubin 1.1 mg., and the fasting blood sugar 81 mg. per 100 ml. The amylase was 4 Russell units, the alkaline phosphatase was 13.5 units, the cephalin flocculation + + +, and the bromsulfalein retention 33 per cent. The prothrombin content was 55 per cent, and the serum cholinesterase activity was 0.56 delta pH per hour. Cytologic examination of gastric fluid for malignant cells was negative. Stool specimens gave negative guaiac tests.

X-ray films of the chest demonstrated medial elevation and some haziness of the right leaf of the diaphragm. An abdominal film showed probable enlargement of the spleen. A cholecystogram demonstrated failure of the gall bladder to concentrate the dye. An intravenous cholangiogram visualized the biliary system faintly; 2 cm. distal to the junction of the right and left hepatic ducts there was an abrupt deflection of the common duct laterally, with widening of the column of contrast material and irregularity of its contour, suggesting flattening in the anteroposterior direction. An upper gastrointestinal series

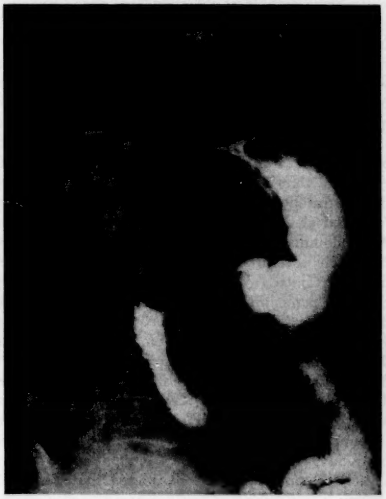

FIGURE 1. *Right Anterior Oblique View of the Stomach. There is an extrinsic pressure defect along the superior aspect of the distal antrum and duodenal bulb.*

demonstrated extrinsic pressure at the cardia of the stomach; the antrum was displaced downward by a curved, extrinsic pressure defect on the lesser curvature that suggested a mass roughly 7 cm. in diameter (Fig. 1); the antrum appeared to be fixed to this mass, but there was no evidence of mucosal ulceration; the duodenal bulb also gave evidence of extrinsic pressure by the same mass; there was a moderate-sized diverticulum arising from the second portion of the duodenum near the ligament of Treitz. Barium-enema examination was negative. An electrocardiogram

showed prominent P waves and nonspecific changes in the ST segments.

The patient improved symptomatically although the liver-function tests remained essentially the same. The temperature ranged between normal and 100°F. On the fourteenth hospital day the spleen and liver were each palpable 3 fingerbreadths below the respective costal margins. Peritoneoscopy at this time revealed normal peritoneal surfaces; the liver appeared slightly granular and slightly yellowish; the gall bladder could not be seen because of adhesions in this area; the anterior surface of the stomach appeared normal; the spleen was enlarged; the other contents of the peritoneal cavity were normal. A biopsy specimen of the liver showed large amounts of hemosiderin, in both the stroma and hepatic cells; there was very little fibrosis.

On the twenty-first hospital day there were shaking chills associated with a rise in temperature to 104.4°F. Rales were audible at the right-lung base. Examination of the abdomen revealed tenderness in the right upper and lower quadrants, without rebound tenderness, and diminished peristalsis. The white-cell count was 12,000. Cultures of the blood grew out coliform bacilli in one flask. A urine culture gave a moderate growth of coliform bacilli. Stool cultures were negative for enteric pathogens and grew out abundant *Staphylococcus aureus*. A throat culture gave a moderate growth of *Staph. aureus*. X-ray films of the chest demonstrated a localized infiltration in the right lower lobe and elevation of both leaves of the diaphragm. An abdominal film showed no definite dilatation of the colon; several air-containing loops of small intestine were noted. With chloramphenicol, erythromycin and penicillin therapy the temperature fell to normal. Two days later the serum nonprotein nitrogen was 41 mg., and the bilirubin 0.8 mg. per 100 ml. The sodium was 122 milliequiv., the potassium 3 milliequiv., and the chloride 89 milliequiv. per liter. The alkaline phosphatase was 8.6 units. The amylase was 2 Russell units. Marked generalized abdominal rebound tenderness was noted on the twenty-fifth hospital day. On the next day the patient appeared acutely ill and vomited bile-stained material. The abdomen was distended and tympanitic, with marked rebound tenderness that was greater on the right side than the left. There was no spasm or localized point of tenderness. No masses were felt. Peristalsis was absent. X-ray films of the chest demonstrated elevation of the diaphragm and evidence of atelectasis in both lower lobes. An abdominal film showed considerable distention of the small intestine. With gastric intubation there was a temporary improvement in symptoms. The temperature was normal, and the white-cell count 12,500. An abdominal film on the twenty-seventh hospital day showed persistent distention of the small intestine and some peritoneal fluid. On the next day the white-cell count was 17,300. The serum nonprotein nitrogen was 95 mg., and the bilirubin 1.5 mg. per 100 ml. The alkaline phosphatase was 7 units. On the twenty-ninth hospital day an abdominal paracentesis yielded 500 ml. of cloudy, yellow fluid that contained a purulent exudate; cytologic examination for malignant cells was negative; culture showed no growth. The temperature rose to 102.8°F., and there were episodes of disorientation. With intestinal intubation there was a decrease in the distention of the small intestine, but there was diarrhea, with passage of a greenish stool that grew out abundant *Staph. aureus* on culture and gave a negative guaiac test. Antibiotic therapy was discontinued, and the diarrhea ceased. Ascitic fluid reaccumulated, and the patient became oliguric. The temperature remained normal after the thirtieth hospital day. The white-cell count rose to 30,000. On the thirty-fifth hospital day the hemoglobin was 10.7 gm. per 100 ml., and the white-cell count 22,100. The serum nonprotein nitrogen was 56 mg., the bilirubin 1.4 mg., and the total protein 5.1 gm. per 100 ml. The sodium was 136 milliequiv., and the potassium 6.5 milliequiv. per liter. The alkaline phosphatase was 9.3 units. The prothrombin content was 50 per cent. On the next day an abdominal paracentesis yielded 1450 ml. of cloudy, yellow fluid that contained numerous neutrophils; cytologic examination for malignant cells was negative. She died on the thirty-seventh hospital day.

Differential Diagnosis

Dr. Joseph Stokes, III*: There are several points in this rather long protocol that are worth emphasis. The illness started with abdominal pain, which was diphasic, starting with episodic colicky pain and then recurring with a different pain in the upper abdomen followed shortly by pain lower in the abdomen. It is also of interest that the patient had had pernicious anemia for fourteen years, which apparently had been well controlled, and that she had taken iron orally. Was the amount and regularity of the oral iron intake over this period known?

Dr. Benjamin Castleman: She ingested a great deal of iron; she took it daily for many years.

Dr. Stokes: On the initial physical examination there was tenderness throughout both upper quadrants; however, exquisite tenderness of the edge of the liver was not present. The temperature was slightly elevated on admission, and the white-cell count initially was only 6000. Was a differential count done?

Dr. Castleman: One done after the patient had been in the hospital for about two weeks, when the white-cell count was 9700, showed 75 per cent neutrophils.

Dr. Stokes: There was minimal chemical icterus on admission. It seems fair to say that the results of the battery of liver-function tests, with the possible exception of the alkaline phosphatase, which was in the range seen with extrahepatic biliary obstruction, were those usually seen in hepatocellular disease of the liver. Perhaps, now is the time to find out what Dr. St. Aubin can contribute to the diagnosis.

*Assistant in medicine, Massachusetts General Hospital.

DR. PAUL M. G. ST. AUBIN: The x-ray film of the chest shows elevation of the right leaf of the diaphragm that is apparently greater in the anterior portion; certainly the right leaf is not as sharply defined as the left. Presumably, there is some abnormal process in the lower-lung field. The remainder of the lung fields are clear; the heart is not remarkable, and the bones are slightly demineralized. On the film of the abdomen there is gas scattered in the colon, with a small amount in the small bowel. A shadow that appears to be the edge of the liver does not appear to be low; the edge of the spleen is denser than usual. The shadow of the right kidney is not as sharp as that of the left, but then there is a great deal of gas overlying it. A series of three gastrointestinal studies revealed the esophagus to be normal. In the region of the cardia, where the fluoroscopist noted a peculiar appearance, what appears to be an indentation with a small shelf is seen. There is extrinsic pressure upon the gastric antrum and the superior aspect of the duodenal bulb. The duodenal loop is normal. The tissue over this region is homogeneous; there is no suggestion of calcification or gas within it.

On the cholecystogram the gall bladder is not visualized. This intravenous cholangiogram shows contrast substance collecting well in the ducts from the right lobe of the liver; those on the left are not well seen, but a rib overlies that area. The man who interpreted the films was taking a great deal on himself to say that this was the common duct. For one thing, it is markedly widened; it reaches over a diameter of 1 cm.; it is in the position of the gall bladder and, indeed, we see a shadow that looks like cystic duct coming from it here. Although it could be the common duct, I should not think that it could be stated with certainty that it is. It could well represent a gall bladder that was only partly filled. The lower aspect of the liver is sharply defined and is denser than usual.

Two films of the chest taken after peritoneoscopy demonstrate that the right leaf of the diaphragm is well separated from the liver, which has a sharp upper margin and has a small amount of air beneath it. The lung fields are moderately clear; there may be slight atelectasis in the lower lobe. The films taken on the twenty-fourth hospital day demonstrate atelectasis in the lower lobe and distention of the small bowel.

DR. STOKES: The initial hospital course was that of relative improvement, and on the fourteenth hospital day peritoneoscopy was performed. At times peritoneoscopy can be an invaluable diagnostic aid; however, in view of the location of the lesion, might it not have been suspected that the lesion would have been hidden from the peritoneoscopist? Perhaps Dr. Benedict will comment on that later.

The biopsy of the liver specimen taken during the peritoneoscopy was interesting in that there were large amounts of hemosiderin in both the stroma and the hepatic cells and very little fibrosis, findings that are compatible with hemochromatosis and explain the increased radiopacity of the liver and spleen. A few years ago Jacobson[1] discussed a case that was termed exogenous hemochromatosis in which a woman who had a mild refractory anemia had taken large amounts of iron over a long period. Dubach and his associates[2] have shown that patients with anemias of varied etiology, including pernicious anemia in relapse, absorb markedly increased amounts of iron from the gastrointestinal tract. It appears that such an increased absorption occurred in this woman and that it had left her with abnormal hemosiderin deposits in at least the liver and spleen. This mild exogenous hemochromatosis may have been responsible for the majority of the abnormal liver-function tests.

On the twenty-third hospital day there was suddenly a change in the patient's course, with shaking chills, a temperature of 104°F. and elevation of the white-cell count for the first time. Coliform bacilli were grown from both the blood and urine, and abundant *Staph. albus* from the stool. The patient was given chloramphenicol, erythromycin and penicillin, which raises the problem of this patient's antibiotic therapy. Superinfection is becoming a greater and greater problem. The three antibiotics used in this case were at one time highly effective against the staphylococcus. Subsequently, however, hospital staphylococci have become increasingly more resistant to all three drugs, and, as illustrated by this case, in spite of five days of therapy abundant *Staph. aureus* were still cultured from a stool and perhaps were responsible for the enteritis. In addition to this problem, treatment with antibiotics can mask symptoms in patients with concealed suppurative foci and make the diagnosis and therapy more difficult.

It also might be noted that the alkaline phosphatase fell, rather than rose, during this stage of the patient's illness. Finally, the clinical picture changed again, with the development of peritoneal signs and a cloudy, yellow, purulent ascitic fluid, which grew out no organisms on culture. Were any organisms seen in a stained smear of the fluid?

DR. CASTLEMAN: Smears done revealed many neutrophils and questionable gram-negative cocci to one observer — a fourth-year medical student.

DR. STOKES: The differential diagnosis in this eighty-year-old woman should start with the possibility of malignant neoplasm. The fact that she had had pernicious anemia for fourteen years raises the possibility of carcinoma of the stomach. Conceivably, this mass could have been a local extension from a small primary tumor in the stomach. I do not know whether Dr. St. Aubin would want to say that this lesion at the cardia could represent a primary carcinoma there. The patient did not have the usual symptoms of gastric carcinoma; there was no anemia and no blood in the stools. These facts, together with the findings on the gastrointestinal series, make that diagnosis seem unlikely.

A pancreatic carcinoma is even more difficult to

fit the clinical picture. As a rule, if the level of amylase changes with pancreatic carcinoma, it is only slightly elevated. In this case the initial amylase was low, and a repeated value still lower. It is conceivable that tumor infiltrating the pancreas could have so completely replaced the organ as to lead to abnormally low amylase levels. However, under these conditions I should think that diabetes could also have been present. In addition there was no x-ray evidence or clear clinical symptoms of a primary neoplasm in either the head or the body of the pancreas.

The patient had hemochromatosis. Is it possible that she had a superimposed primary liver-cell carcinoma? The major factor against this diagnosis is the normal findings at peritoneoscopy; such a tumor should have been visible through the peritoneoscope, since it is often more focal or spreads rapidly through the liver.

Carcinoma of the gall bladder and carcinoma of the bile ducts, cholangiocarcinoma, both should be considered, particularly in view of the relation of the mass to the common duct. Unremitting jaundice, which is the earmark of these diseases, was not present. Therefore, these possibilities can be excluded.

Echinococcus disease should also be considered. It is not stated how many of her eighty years the patient spent in Massachusetts, which certainly is not an endemic area for this disease. It would be difficult to explain all the findings by a hydatid cyst, although it may occur in the area occupied by this mass.

The absence of any past intestinal complaints or a past history of amebiasis does not exclude amebic abscess of the liver. Although the clinical picture would be unusual for that disease, it cannot be excluded.

It seems most likely that this patient suffered from a manifestation of cholecystitis, and her illness can be reconstructed as follows: six weeks before admission she had an episode of cholecystitis with a perforation that was well localized; over the subsequent six weeks the pus dissected into the subhepatic space and gave rise to an abscess seen as a mass on the x-ray films. Subphrenic dissection seems excluded by Dr. St. Aubin's demonstration of the clear area over the diaphragm when air had been introduced during peritoneoscopy. The abscess gave rise to a transient bacteremia, and, later, there was local leaking of the material into the general peritoneal cavity with the development of generalized peritonitis although masked by the antibiotic therapy, which eventually led to death. The appendix or pancreas cannot be excluded as the primary site of the infection, but the gall bladder seems more likely. In addition the patient had exogenous hemochromatosis.

DR. EDWARD B. BENEDICT: I should like to ask Dr. Stokes if he is postulating another mass besides the one in the liver and spleen. Is there evidence for another mass?

DR. STOKES: I do not think that the mass demonstrated was in the position of the liver.

DR. BENEDICT: Does Dr. St. Aubin think there is a mass separate from the liver?

DR. ST. AUBIN: I can outline a sharp right edge of the liver. I do not see how one can say that the liver was not impressing the stomach, particularly a mass of the left lobe. It could be a mass on the left lobe of the liver. I am very much disturbed about this case; I think that the patient had carcinoma of the stomach.

DR. BENEDICT: All I could see through the peritoneoscope was a large, yellow liver without nodules; I did not expect more than that. We were asked to do the peritoneoscopy to look at the liver. There may have been nodules of neoplasm inside the liver or on the surface that could not be seen through the peritoneoscope, so that the findings at peritoneoscopy do not rule out neoplasm.

DR. CASTLEMAN: You did not see implants anywhere on the peritoneum, and you thought that the liver looked cirrhotic; is that correct?

DR. BENEDICT: There were no implants. The liver was yellow and granular; we could not make a diagnosis and said, "question of hepatitis and question of cirrhosis."

DR. CASTLEMAN: Have you an alternative diagnosis, Dr. Harwood?

DR. REED HARWOOD: I wonder vaguely about another type of tumor — leiomyosarcoma of the stomach.

DR. HELEN S. PITTMAN: I shall go along with the theory that this patient had empyema of the gall bladder.

DR. JACOB LERMAN: I, too, would consider ruptured gall bladder, with abscess that had become diffuse.

DR. BENEDICT: I thought that Dr. Stokes implied that all the trouble began with the peritoneoscopy. I do not deny that we may have introduced air and infection at the time of peritoneoscopy, but the temperature had been 100°F. before, and the serious rise did not occur until a week after the peritoneoscopy.

DR. STOKES: I did not mean to imply that. My only question was whether, in view of the way in which the mass displaced the stomach on the x-ray film, you could have predicted that it would not be visible through the peritoneoscopy. It appears to be so far posterior that it might be covered by adhesions.

DR. BENEDICT: The physicians asked us to look at the liver. The problem of a separate mass was not presented to us. I never expect to see anything that is not on the surface.

DR. CASTLEMAN: You did not find any ascitic fluid?

DR. BENEDICT: No; we did not at that time, but we did see adhesions, which prevented us from visualizing the gall bladder. The adhesions, I think, lend support to the theory.

CLINICAL DIAGNOSES

Peritonitis.

Pernicious anemia.
Hemochromatosis.

Dr. Joseph Stokes, III's, Diagnoses

Cholecystitis, with perforation of gall bladder and abscess formation.
Hemochromatosis, exogenous.

Anatomical Diagnoses

Adenocarcinoma of gall bladder, with metastases to liver, diaphragm and lymph nodes.
Cholelithiasis.
Acute and chronic cholangitis.
Abscess of liver.
Thrombosis of portal vein.
Ascites.
Hemosiderosis of liver and spleen.
Pernicious anemia.

Pathological Discussion

Dr. Castleman: At autopsy we found 5 liters of ascitic fluid, which was slightly turbid but not infected. We were unable to see evidence of a true peritonitis on the surface of the bowel. There were no abscesses in the peritoneal cavity. The mass proved to be metastatic carcinoma, protruding from the left lobe of the liver and producing the defect seen on the x-ray films. There were other nodules of tumor within the liver; one on the left had broken down and become an abscess. Dr. Benedict, we found the biopsy site; if you had gone down 2 mm. more you would have entered the carcinoma. We actually measured the distance. There were no nodules on the surface. The bulk of the tumor was at the porta hepatis and surrounded the portal vein, infiltrating its wall and producing thrombosis of the portal vein. The thrombosis, which was quite recent, extended in both directions: up both intrahepatic portal-vein radicles into the liver and down to the mouths of the superior mesenteric and splenic veins. Grossly, it seemed to be completely occluding the mouth of the superior mesenteric vein, so that we wondered why there was no infarction of the bowel. The microscopical sections, however, showed that there was recanalization, which apparently allowed blood to pass.

The primary tumor was in the gall bladder, which contained a stone. The infiltration of the tumor in the gall-bladder wall extended into the surrounding liver and formed a good-sized nodule there, as well. The cause of the ascites, which appeared quite suddenly, was probably the thrombosis of the portal vein, for the ascites was not present previously. There was no infection in the ascitic fluid; the cells that it contained were necrotic tumor cells, so that I think we can exonerate Dr. Benedict from producing peritonitis. The tumor had also involved the right leaf of the diaphragm but was not adherent to it. Microscopically, the liver showed a great deal of cholangitis, a little fibrosis and extensive deposits of iron pigment. I should not call it a true hemochromatosis but rather hemosiderosis; I believe that the fibrosis was produced by the obstructive phenomenon as the result of the gall-bladder disease.

The tumor microscopically was a not too well differentiated adenocarcinoma. The thrombus in the portal vein was not tumor thrombus but was secondary to the obstruction caused by the tumor.

Dr. Stokes: I should have mentioned that the white-cell count of 6000 on admission was the significant point against the diagnosis of an abscess. If that large an abscess had been present, the white-cell count should have been higher.

Dr. St. Aubin: Did you examine the stomach?

Dr. Castleman: The stomach was normal.

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CASE 42432

Presentation of Case

An eighteen-year-old single colored girl was admitted to the hospital because of paralytic poliomyelitis.

Seven days previously she noted severe, generalized, throbbing headaches, as well as postprandial episodes of severe crampy pain in the lower anterior portion of the chest. Subsequently, there was malaise, anorexia and weakness. Four days before entry she was admitted to another hospital, where she was placed in a respirator.

She had had one menstrual period when she was eight and another that lasted for a month at the age of thirteen. There were no subsequent periods. When the patient was two months old her mother had died of tuberculosis.

Physical examination showed a normally developed, well nourished girl who was in no acute distress but occasionally complained of crampy pain in the lower anterior portion of the chest. The voice was feminine, the breasts were normally developed, and there was a female distribution of hair, although it was somewhat excessive. Examination of the chest was negative. The abdomen was tympanitic and slightly distended. No masses were felt. Slight tenderness was noted in the epigastrium and left side of the abdomen. Normal bowel sounds were audible. Neurologic examination revealed motor weakness in the left arm, left leg and thigh. Except for the ankle jerk, the deep tendon reflexes were absent on the left side. There was weakness of grasp on the right. Sensory examination was negative.

The temperature was 98°F., the pulse 88, and the respirations 30. The blood pressure was 125 systolic, 80 diastolic.

The urine gave a ++ test for albumin; the sediment contained 5 red cells and 125 white cells per high-power field; culture of a catheterized specimen grew out abundant coliform bacilli. The 17-ketosteroid excretion was 5.8 mg. per twenty-four hours. Examination of the blood revealed a hemoglobin of 12.2 gm. per 100 ml. and a white-cell count of 4800. The vital capacity after one hour outside the respirator was 550 ml.

There was a gradual return of motor power in the limbs, and the patient became able to breathe without the respirator. Gantrisin therapy was given. The temperature remained normal. Intermittent episodes of pain in the chest and epigastric discomfort that usually occurred after eating continued. On the thirtieth hospital day there was a postprandial episode of diffuse abdominal pain and pain in the chest that was more severe than that previously noted. The pain did not radiate, and there was no nausea or vomiting. The abdomen was soft, with tenderness in the right lower quadrant, where there was subsequently rebound tenderness. Rectal examination revealed tenderness on the right side. The temperature and pulse were normal. The white-cell count was 10,500. The urine gave a + test for albumin; the sediment contained 3 to 5 red cells, 5 to 7 white cells and a few bacteria per high-power field; a culture gave a moderate growth of nonhemolytic streptococci. During the next three days the abdominal tenderness increased, with slight guarding and marked rebound tenderness. Dysuria was noted. The white-cell count rose to 16,600. The temperature rose to 101.6°F. by rectum, and the pulse rose to 116. An x-ray film of the abdomen demonstrated distended loops of small intestine in the left side of the abdomen; the kidney and psoas shadows were not clearly defined. On the thirty-third hospital day the abdominal pain became localized to the right lower quadrant, and rebound tenderness was referred to this region. There was no spasm. Peristalsis was normal. Rectal examination revealed fullness high on the right, with tenderness that was more marked on the right than the left. One observer felt a mass on the right.

On the thirty-fourth hospital day an operation was performed.

Differential Diagnosis

Dr. Janet W. McArthur*: May we begin by seeing the x-ray films?

Dr. Joseph Hanelin: No obvious masses are apparent, nor is there any indication of extrinsic pressure upon any portion of the gas-filled bowel. The patient was obviously quite thin, and lack of intra-abdominal fat makes it impossible adequately to delineate visceral structures. This may be the basis for the over-all increased density overshadowing the true pelvis, although there is the additional possibility of an abnormal mass or fluid in this area. Gas-filled loops of small bowel, which are not significantly distended, are visible in the upper abdomen and to the left of the lumbar spine. Gas and fecal matter are observed in the rectum, and the cecum is similarly outlined and is in normal position.

Dr. McArthur: The crux of the problem presented by this patient is the origin of a series of attacks of abdominal pain that occurred during hospitalization for paralytic poliomyelitis and ultimately led to operation.

It seems permissible to pass rapidly over the neurologic findings and the urinary infection, for both of which the poliomyelitis appears to account adequately. Atonicity of the bladder, with symptoms varying from difficulty in initiating urination to complete retention, occurs frequently during the acute stage of poliomyelitis. This necessitates catheter drainage, with the attendant hazard of secondary infection.

The oligomenorrhea appears deserving of more careful scrutiny. Although menstruation had begun precociously when this patient was eight years of age, only one period had occurred in the subsequent ten years. Since an early menarche ordinarily indicates high reproductive vitality, the occurrence of secondary amenorrhea of such severity suggests the prolonged operation of some counteracting force. For this reason I shall concentrate on chronic disorders that could account for both the oligomenorrhea and the subsequent pain, and shall summarily dismiss such acute entities as appendicitis, mesenteric adenitis, Meckel's diverticulitis, rupture of a follicle and ectopic pregnancy.

One such chronic disorder suggested by the history is that when the patient was two months old her mother died of tuberculosis. Although it is often stated that the frequency of amenorrhea and oligomenorrhea in tuberculosis has been overemphasized, amenorrhea was observed in 6.5 per cent and oligomenorrhea in 20 per cent of Greenberg's[1] series of 200 patients with tuberculous salpingitis. A history of preceding gastrointestinal distress and of abdominal pain intensified in the right lower quadrant has occasionally led to operations for acute appendicitis upon patients who proved to have genital tuberculosis.

We are told nothing about this patient's health in the years preceding the onset of paralytic poliomyelitis, but she is described as normally developed and well nourished. Although occasional patients with genital tuberculosis are reputed to enjoy good general health, the majority suffer from constitutional symptoms, such as lassitude, malaise, anorexia, flatulence, constipation, unexplained afternoon fever and loss of weight. These ordinarily persist for years and are out of proportion to the pelvic findings. Lacking positive evidence that suggests the presence of either genital or extragenital tuberculosis, I shall discard this possibility.

Endocrinopathies constitute another category of

*Assistant physician, Massachusetts General Hospital.

disorders that could depress menstrual function and that, under certain circumstances, could culminate in acute abdominal pain. The patient was not virilized, as evidenced by the feminine pitch of her voice and the absence of such abnormalities as clitoral hypertrophy, baldness and temporal recession of the hairline. However, the hair distribution, which is described as female but "somewhat excessive," evidently attracted enough attention to result in the performance of a 17-ketosteroid determination. The result obtained, 5.8 mg. per twenty-four hours, may have been slightly lower than the true value because of the preceding infection. However, even if one allows for this factor, it seems unlikely that there can have been a genuine increase in the 17-ketosteroid excretion. This tends to exclude adrenocortical hyperplasia and tumor and to fix attention upon the ovary. A normal level of 17-ketosteroid excretion may be associated with such defeminizing tumors as the hilus-cell tumor and arrhenoblastoma and is characteristic of the Stein–Leventhal syndrome.

Of these three conditions, I shall immediately discard the hilus-cell tumor because of the comparatively advanced age of the patients with this condition reported to date. There are a few well authenticated cases of arrhenoblastoma in which even hirsutism was lacking.[2,3] However, in the great majority of patients with this rare tumor, not only hirsutism but also frank virilism develops. The Stein–Leventhal syndrome is a more attractive possibility because of the fact that many patients with this condition never become hirsute or do so only during late adolescence.

In these exercises it is not uncommon for the diagnosis to hang by a hair. Accordingly, I shall discard the diagnosis of arrhenoblastoma in favor of the Stein–Leventhal syndrome and postulate that this patient's oligomenorrhea was due to the presence of large, pale polycystic ovaries. Subsequently, the right ovary suffered the accident of torsion, which may have been intermittent and which, in any event, was gradual enough to produce pain without nausea, vomiting or shock.

Clinical Diagnosis

Perforation of appendix, with walled-off infection.

Dr. Janet W. McArthur's Diagnoses

Stein–Leventhal syndrome.
Torsion of right ovary.

Anatomical Diagnoses

Torsion, with hemorrhagic infarction, right ovary.
Stein–Leventhal syndrome.

Pathological Discussion

Dr. Leonard Atkins: Dr. Coe, will you describe your findings at operation?

Dr. Robert C. Coe: This girl had had an attack of abdominal pain for three days when we first saw her, and presented all the findings of an inflammatory process in the right lower quadrant. The presence of a mass led us to believe that the appendix had perforated and become walled off; since the course had been one of inability to control the sepsis, it seemed wise to explore her with a preoperative diagnosis of acute appendicitis with probable perforation. We were greeted with a tremendously enlarged, necrotic right ovary, which presented itself in the lower abdomen, rather than in the pelvis. Through a right paramedian incision the left ovary was easily visualized and was found to be large, pale and polycystic. Then, for the first time, we became aware of the diagnosis of Stein–Leventhal syndrome, with a torsion of the right ovary. This was excised; the left ovary was wedged, and the multiple cysts perforated.

Dr. Atkins: The right ovary, which was markedly hemorrhagic, weighed 110 gm. and measured 8.5 cm. by 6 cm. by 4 cm. It contained a large, ill defined, cystic space that measured 3.5 cm. by 1.2 cm. by 0.5 cm. In addition, four other cysts, varying from 2 mm. to 4 mm. in diameter, were present. Microscopically, the architecture appeared completely destroyed by hemorrhage and necrosis. The wedge of left ovary that was removed measured 3.5 cm. by 3.5 cm. by 0.8 cm. It was yellow white, with a smooth, glistening surface. A cyst that measured 2 mm. in diameter was noted beneath the capsule. Microscopically, the tunica albuginea was thickened and sclerotic, and several small follicle cysts lined by prominent thecal cells were seen. There were no corpora lutea. These are the characteristic findings of the Stein–Leventhal syndrome.

Dr. Quentin Stiles: About two months postoperatively the patient reported that she had a normal period.

Dr. Robert E. Scully: This is the first case of torsion of a polycystic ovary that I have seen. Dr. Francis M. Ingersoll, however, tells me that in the series of cases of Stein–Leventhal syndrome reported by McDermott and him,[4] 1 was complicated by torsion. In that case the ovary was not yet infarcted; the twist was reduced, and bilateral wedge resection was done. We know that an ovary that appears to be normal rarely twists; it is not surprising, then, that the heavy polycystic ovary of the Stein–Leventhal syndrome should occasionally do so.

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THE ORDER CHANGES

AN obscure notice in the issue of the *Journal* of September 27 announced to its readers the impending dedication on October 5 of the new Children's and Infants' Hospital Building of the Boston Children's Medical Center. This momentous change serves also as a reminder of what has gone before and what has been replaced.

Many pediatricians and other physicians the country over remember with little less than awe the original Infants' Hospital of white marble, erected as a memorial to Thomas Morgan Rotch and now the Harvard School of Public Health, located strategically on what has become Shattuck Street, behind the Children's Hospital. It was replaced by a pavilion still more intimately associated with the larger institution, and now this, too, is gone; a salute to its rubble is in order, for it not only witnessed the advent of the modern era of pediatrics, but housed many of the pioneering studies that helped make that era.

The Hospital's curtain rose, so to speak, at a time when "percentage feeding" was a sacrosanct ritual, presided over by Rotch and Morse to the obfuscation of the medical student, and if any bold spirits vaguely sensed that an "acute nutritional disturbance" might be due to an infection of the infant rather than to the carbohydrate content of the formula, they kept their doubts discreetly to themselves. From such an atmosphere Talbot and Smith escaped to the less confusing climate of the Massachusetts General Hospital. At the time one of the hallmarks of the pediatrician that distinguished him from the general practitioner was that he looked into a baby's ears. If the drums were inflamed, a paracentesis was done as early as possible to promote drainage and thus to circumvent bulging, suppuration and mastoiditis.

A pediatrician was also distinguished because he routinely examined the urinary sediment and thus often picked up pyelitis as a cause of unexplained fever. Acute overwhelming tracheobronchitis was frequently treated by tracheotomy if the patient came first under otolaryngological supervision, and more conservatively if he happened to come first to the medical service. The outcome was probably about as good for the radicals as for the conservatives. These were the days, long before antibiotics had made their appearance, when the victories of medicine were due more to good nursing care and the "vitality" of the patient than to specific therapy, transfusions and immunizations. They were also the days when there were plenty of babies to demonstrate that the rachitic rosary was to be distinguished from the sharper scorbutic variety by the character of its contour; when acrodynia was good for two hours of grand rounds on any day.

Pediatrics had just settled into its place as one of the major branches of medicine when Dr. Kenneth Blackfan took over the direction of the Infants' as

well as of the Children's Hospital. There, he and Yaglou made their basic physiologic studies of premature babies. Air-conditioning equipment was installed in the basement, and used to evaluate the effects of regulating environmental temperature and humidity in the nurseries above. Another pioneering venture in the basement of the Infants' Hospital was the respiration chamber designed by Professor Philip Drinker and Dr. James Wilson, so that a group of children could be cared for by one nurse working inside the submarinelike room, the atmosphere of which could be varied at will.

On the floors above came many a baby with many a bizarre disease — illnesses the like of which were not found in internal medicine. These were the illnesses that were to make pediatrics a specialty in its own right, and the pathogenic mechanisms were slowly to be unraveled in the course of years by old hands and by youngsters alike. Many in due time became dignified and reputable professors or associate professors themselves — Alan Butler, Alfred Shohl, Louis Diamond, James Baty, Fred Robbins — the list is long and omissions are inevitable, nor does any listing take into account the great and the near-great who did not belong primarily to the Infants' Hospital. They came to visit or to consult as roentgenologists, pathologists, surgeons or orthopedists — "B" Ladd, Burt Wolbach, Ed Vogt, Jim Gamble, Bill Green, John Enders and the rest. Their first names were as much the property of the youngest student (out of hearing) as they were of the eldest elder statesman.

Nor do the names of human beings alone tell the story unless they are coupled with concepts of pathologic processes like icterus gravis, pyloric stenosis, celiac disease, electrolyte imbalances, vitamin deficiencies and three kinds of poliomyelitic infection. As with the numbers of physicians who taught and learned and struggled with the humdrum problems of the day, the list of diseases is too long to be printed in a text of this nature. The list, like the art, is long; the life of the building, like the life of a man, was short. And yet, in its own inanimate way, the building also lived, and its passing should not be unnoticed or unmourned.

NATIONAL COUNCIL ON INFANT AND CHILD CARE

ORIGINATED under excellent auspices, the establishment of a new, independent and forward-looking country-wide organization for the promotion of health has recently been announced. This is the National Council on Infant and Child Care — unfortunately abbreviated to NCICC and thereby forced into the ghostly legion of alphabetic anonymity — with headquarters in the New York Academy of Sciences Building, with Dr. Allan M. Butler, of Boston, as president and with a group of acknowledged leaders in the pediatric field as officers and members.

This particular national council will concern itself with a serious attempt at directing, in its own field, that new, overwhelming force in the scientific and not so scientific world — the Juggernaut of communication. Recognizing the momentum that this prodigious vehicle has acquired up to the present instant, these individuals, who are chiefly occupied with child health and welfare, will direct their efforts "to foster the presentation of medical knowledge to the public in a manner appropriate to the best medical standards" and to "encourage truthful, informative promotion of products that are important to child health."

By definition the Council is a nonprofit organization designed for the purpose of giving practical counsel on matters within its purview. The need is based on the appalling increase in the mediums of communication, as previously indicated; on the confused and confusing bulk of medical lay literature; and on the constantly augmented number of pharmaceutical preparations that are promoted directly or indirectly to the public. To combat these tendencies the Council plans to make available accurate information to writers and editors for dissemination to the public. This will be accomplished, according to the prospectus, by providing information to medical science writers; by reviewing lay medical articles, on request; by checking and consulting on advertising of pharmaceutical and other products relating to child health; by publishing appropriate material, and by promoting sound and effective medical, industrial and public relations.

In addition to the provision of medical information, the publication of material on infant and child care and a consultation service to all those engaged in the publicizing of medical information, whether by radio, television or the written word, the Council has under consideration a program of awards to writers and editors.

The total mission is ambitious, but it is being undertaken earnestly and with a real need in view. Since the child is father to the man perhaps this reform will spread from a concern with the infant and the child to embrace the five remaining ages of mankind.

THE *VETERINARIAN*

IN company with the names of the Scottish dead of two wars, looking down from the walls of Scotland's stately War Memorial, capping the highest ledge in Edinburgh Castle, appear the bas-reliefs of others that served and often died in the same common cause. They depict and will commemorate, as long as such memorials shall last, the horses and dogs and donkeys, the mules and the camels, the pigeons and mice and elephants, and all the other birds and beasts that went to war, on the field or in the laboratory, willingly or reluctantly, like the men they served.

It is a moving reminder, not only of the multiple ways in which so many of the creatures here below have been put to man's labor, but of the comradeship and mute devotion that some of them have given with that labor.

A consideration of the animals that have served mankind is incomplete without a consideration of the men that have served the animals, from the shepherd on the hills to those "trained in the science and art dealing with the prevention, cure, or alleviation, of disease and injury in animals" — the doctors of veterinary medicine.

It is with a sense of fraternal endeavor, therefore, that the editors of the *Journal* extend to those nonsectarian disciples of Assisi who make up the membership of the Massachusetts Veterinary Association congratulations on the first number of their own quarterly journal, the *Veterinarian*.

BREAD UNLEAVENED

A YOUNG woman physician, health officer of the Florida counties of Jefferson, Taylor and Madison, is reported to have been dismissed from her post for having eaten lunch at a business conference with a Negro midwife consultant to the state board of health. The conference was held in the private dining room of a restaurant.

The professional services of Dr. Deborah Coggins were praised; the dismissal was on the basis of her action's having "lost her the respect of the people and made her work useless." The Ku Klux Klan of Palatka is said to have wholeheartedly endorsed the action taken against Dr. Coggins, although Governor Rollins, in severely criticizing the commissioners, declared that "it cannot be squared with right and justice and conscience."

Since the Last Supper the breaking of bread has had a peculiar significance, especially for Christians, although the act appears to have been generally associated with mercy, humility, compassion and brotherhood.

Almost simultaneously with the report from Florida came a release from Simpson College, in Indianola, Iowa, which on October 6 dedicated its new Carver Science Hall in honor of the institution's famous Negro alumnus, George Washington Carver. The memorial address was given by Ralph J. Bunche, undersecretary of the United Nations, on the subject, "The World Significance of the Carver Story."

Professor Carver was admitted to Simpson in 1890 after being refused admission at another college because of his race, and it was here that his life work, of such incalculable benefit to the agricultural South, began. Here, also, he is said to have made his greatest discovery, "that I was a human being."

The Sultan has authorized the formation of a Medical Society at Constantinople, and has sanctioned its title as the Imperial Medical Society of Constantinople. The new Institution was started by the English medical men at Scutari — Charleston Medical Journal and Review.

Boston M. & S. J. *October 30, 1856*

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

Orthopedic Clinic	Date	Clinic Consultant
Greenfield	November 1	Charles L. Sturdevant, M.D.
Lowell	November 2	Albert H. Brewster, M.D.
Salem	November 5	Paul W. Hugenburger, M.D.
Haverhill	November 7	William T. Green, M.D., and Henry Banks, M. D.
Brockton	November 8	George W. Van Gorder, M.D.
Worcester	November 16	John W. O'Meara, M.D.
Gardner	November 19	Carter R. Rowe, M.D.
Lynn*	November 19	Daniel J. Killoran, M.D., and John J. Crowley, M.D.
Pittsfield	November 21	Edward J. Coughlin, Jr., M.D.
Fall River	November 26	David S. Grice, M.D., and Arthur W. Trott, M.D.
Springfield	November 27	James D. Fisher, M.D.
Hyannis	November 29	Paul L. Norton, M.D.

Rheumatic Fever Clinics	Dates
North Reading	November 6, 13, 20, 27
Fitchburg	November 7, 14, 21, 28

Plastic Clinics	Held	Consultant
Eastern Massachusetts	Semi-monthly	Bradford Cannon, M.D., and Joseph E. Murray, M.D.
Western Massachusetts	Monthly	Joseph M. Baker, M.D.

Physicians referring new patients to clinic should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

*This clinic serves Lynn, Lynnfield, Saugus, Nahant, Revere, Chelsea, Everett and Winthrop. Referrals should be made directly to the Lynn Clinic.

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR SEPTEMBER, 1956

RÉSUMÉ

Disease	September 1956	September 1955	Seven-Year Median
Brucellosis	0	2	1
Chancroid	1	1	2
Chicken pox	149	59	85
Diphtheria	1	0	1
Dog bite	1221	1229	1064
Dysentery, bacillary	4	24	11
Encephalitis, infectious	11	2	1
German measles	139	35	48
Gonorrhea	205	154	198
Granuloma inguinale	0	0	0
Hepatitis, infectious	23	65	54
Lymphogranuloma venereum	0	0	0
Malaria	0	1	2
Measles	28	48	62
Meningitis, meningococcal	2	4	3
Meningitis, Pfeiffer bacillus	2	0	2
Meningitis, pneumococcal	1	1	1
Meningitis, staphylococcal	0	0	0
Meningitis, streptococcal	0	0	0
Meningitis, undetermined	24	4	3
Mumps	191	90	173
Poliomyelitis	20	1013	188
Salmonellosis	47	20	13

Scarlet fever	50	44	57
Syphilis	164	161	135
Trichinosis	2	1	3
Tuberculosis, pulmonary	139	147	185
Tuberculosis, other forms	5	8	8
Typhoid fever	2	0	2
Whooping cough	57	55	186

Comment

Diseases below the seven-year median were bacillary dysentery, infectious hepatitis, measles, poliomyelitis, scarlet fever and whooping cough.

During September, the incidence of both bacillary dysentery and infectious hepatitis was at the lowest level for this month since 1951.

During September, the incidence of poliomyelitis was at the lowest level since 1942.

With but one exception (1955) scarlet fever and whooping cough were at their lowest levels for this month in the history of the State.

Diseases above the seven-year median were chicken pox, infectious encephalitis, German measles, mumps and salmonellosis.

During September, the incidence of chicken pox, German measles and salmonellosis were at their highest points for this month in the history of the State.

The marked rise noted in the incidence of infectious encephalitis was due to cases of the eastern equine type.

Geographic Distribution of Certain Diseases

The following diseases were reported from the communities named:

Diphtheria: East Bridgewater, 1.

Dysentery, amebic: Lynn, 1.

Dysentery, bacillary: Bedford, 1; Framingham, 1; Worcester, 2; total, 4.

Encephalitis, infectious: Boston, 1; Brockton, 3; Lawrence, 1; Lincoln, 1; Middleboro, 1; Quincy, 1; Sandwich, 1; Springfield, 1; Walpole, 1; total, 11.

Hepatitis, infectious: Arlington, 8; Boston, 1; Braintree, 1; Cambridge, 1; Fall River, 2; Ludlow, 1; Malden, 1; Medford, 2; Sheffield, 2; Springfield, 2; Worcester, 1; Worthington, 1; total, 23.

Meningitis, meningococcal: Holyoke, 1; North Adams, 1; total, 2.

Meningitis, Pfeiffer bacillus: Beverly, 1; Holyoke, 1; total, 2.

Meningitis, pneumococcal: Boston, 1.

Meningitis, mumps: Belmont, 1.

Meningitis, undetermined: Boston, 4; Brookline, 2; Chelsea, 1; Chelsea Naval Hospital, 1; Chicopee, 1; Easthampton, 1; Hingham, 1; Hull, 1; Mansfield, 1; Marlboro, 1; Newton, 3; Sharon, 1; Somerville, 1; Stow, 1; Watertown, 1; Williamstown, 1; Woburn, 1; Worcester, 1; total, 24.

Poliomyelitis: Boston, 1; Braintree, 1; Brockton, 1; Cambridge, 2; Dedham, 1; Framingham, 1; Holyoke, 1; Lynn, 1; Medford, 1; Montague, 1; Newton, 1; Orleans, 1; Plymouth, 1; Quincy, 2; Salem, 1; Waltham, 1; West Boylston, 1; Worcester, 1; total, 20.

Psittacosis: Natick, 1.

Salmonellosis: Arlington, 1; Boston, 5; Cambridge, 3; Clinton, 1; Danvers, 2; Fitchburg, 2; Framingham, 1; Lawrence, 1; Lexington, 1; Lowell, 1; Lunenberg, 1; Lynn, 1; Lynnfield, 1; Marblehead, 1; Melrose, 2; Middleton, 1; New Bedford, 1; North Attleboro, 1; Northboro, 1; South Hadley, 2; Sterling, 3; Topsfield, 1; Waltham, 1; Wellesley, 2; West Bridgewater, 1; Winchester, 1; Worcester, 8; total, 47.

Tetanus: Brockton, 1.

Trichinosis: Lawrence, 1; Somerville, 1; total, 2.

Typhoid fever: Plymouth, 1; Worcester, 1; total, 2.

CORRESPONDENCE

REGARDING DISEASES OF BONE

To the Editor: The Medical Progress report, "Pathology: Diseases of bone," by Louis Lichtenstein in the August 30 issue of the *Journal* presents the subject in his usual concise and lucid style. I am compelled, however, to call attention to two misquotations. On page 429 he states, "The thesis advanced by Geschickter and Copeland and by Dwinnell, Dahlin and Ghormley, however, that *all* bulky lesions of parosteal ossification represent low-grade sarcomas from their inception and should be treated by prompt amputation even in the absence of unequivocal histologic evidence of malignant change, seems to be an unjustified, rather extreme point of view." On page 431 he states, "The position taken was one of opposition to indiscriminate radical surgery, advocated recently by Geschickter and Copeland and by Dwinnell, Dahlin and Ghormley."

Carefully reviewing the truly great contribution by Geschickter and Copeland on parosteal tumors of bone in the June, 1951, issue of *Annals of Surgery* (133:790-807), I can find no evidence that they recommended "indiscriminate radical surgery" for lesions not proved to be malignant, nor do they say or imply that "*all* bulky lesions of parosteal ossification represent low-grade sarcomas from their inception and should be treated by prompt amputation even in the absence of unequivocal histologic evidence of malignant change." Likewise, the paper by Dwinnell, Dahlin and Ghormley in the *Journal of Bone and Joint Surgery* (36A:732-744, July, 1954) does not support either of these quotations, since these authors discuss a differential diagnosis of parosteal tumors and their statement regarding amputation applies to parosteal sarcomas.

Although parosteal osteogenic sarcomas may contain only minimal evidence of malignant change, this is not synonymous with equivocal evidence of malignant change as Lichtenstein implies. In this rare and difficult group of tumors, it requires a truly "experienced observer" to rule out the benign lesions that simulate parosteal osteogenic sarcoma. This recently delimited and characteristic type of osteogenic sarcoma will undoubtedly be recognized in the next edition of Lichtenstein's book on bone tumors.

D. C. Dahlin, M.D.

Rochester, Minnesota

Note: A copy of Dr. Dahlin's letter was sent to Dr. Lichtenstein, who notes that since he did not quote directly from the paper of Dwinnell, Dahlin and Ghormley he could not have misquoted it. He did interpret the sense of the paper and the message it may convey to surgeons, and it is this, he believes, to which Dr. Dahlin objects. The reasons for his own views are contained in reference 24 to his paper (Lichtenstein, L. Tumors of periosteal origin. *Cancer* 8:1060-1069, 1955). — Ed.

HAZARDS OF MASSIVE BLOOD TRANSFUSIONS

To the Editor: At the recent joint meeting of the International Blood Transfusion Congress and the American Association of Blood Banks in Boston, papers dealing with the hazards of massive blood transfusions were delivered. Transfusionists and hematologists have become increasingly aware of these dangers. This letter is written to remind all physicians who may be concerned with the care of patients needing so many transfusions in so short a period as to be equivalent to an exchange transfusion (an order of magnitude of 10 or more pints) of the difficulties that may ensue and the steps that may be taken to obviate these difficulties or to alleviate them once they have occurred. In summary these dangers are citric acid intoxication, thrombocytopenia and circulatory overload.

Bunker, at the Massachusetts General Hospital, has demonstrated that the rapid administration of large amounts of citrated blood may cause a dangerously high blood concentration of citric acid, with severe hypocalcemia. This cannot be readily controlled by the simultaneous administration of calcium and is particularly hazardous in patients with severe liver disease because of their inability to metabolize citrate. It is also likely to occur after extremely rapid transfusions of large amounts of citrated blood in patients undergoing cardiovascular surgery. Citric acid intoxication from citrated blood can be avoided by the use of citrate-free blood collected by passage through a cation-exchange resin, which makes the blood noncoagulable by removing the calcium. Blood so collected has a short survival period, and if not used within one or two days after collection, this blood must be discarded.

The second hazard from massive whole-blood transfusions has been described by Krevans, of Johns Hopkins Hospital, Stefanini, of St. Elizabeth's Hospital in Boston, and Zucker and her co-workers, of the Sloan–Kettering Institute in New York City. The first two authors demonstrated that such transfusions caused a significant thrombocytopenia, which was not prevented by the use of nonwettable transfusion equipment. A similar thrombocytopenia developed in infants with erythroblastosis fetalis who received exchange transfusions. It was also demonstrable in dogs; in this animal, the transfusion of fresh blood did not cause a significant drop in platelets, but similar blood collected through an ion-exchange column was followed by thrombocytopenia in the recipient dog, presumably because of absorption of platelets by the exchange resin. The reduction of platelets in many patients was often manifest by generalized hemorrhage during or after surgery, and purpura. Some patients after massive transfusions showed not only thrombocytopenia but also increased fibrinolysis, reduced labile-factor activity and low plasma fibrinogen. The cause of the thrombocytopenia is obscure, but several mechanisms have been suggested, including a dilution of platelets in the recipient with nonviable platelets from stored blood, and a platelet-depressing factor that may be present in normal plasma of stored blood. Platelet deficiencies induced by massive transfusions may be corrected by the use of fresh blood, drawn through nonwettable tubing into nonwettable containers, or by the administration of viable platelets or platelet material.

Overloading the circulating blood volume by massive transfusions is an obvious hazard but one that cannot readily be avoided except by frequent determinations of the circulating whole-blood volume and transfusions in accordance with such a demonstrated need. This danger can be reduced considerably by the use of packed or sedimented red cells instead of whole blood, with a consequent reduction in the amount of transfused fluid.

These newly realized problems created by the massive transfusions of whole blood place an additional and arduous burden on all blood banks, and one that cannot be met without the active co-operation of the physician or surgeon responsible for the care of the patient. The obtaining of adequate numbers of donors who can be bled properly and promptly at *hospital blood banks*, so that the patient can get blood that is best for dealing with the situations outlined above, is a joint responsibility of the patient's physician and the blood bank that should not be delegated entirely to blood banks whether hospital or Red Cross, until these agencies have developed an efficient organization for the quick procurement of compatible "blood on the hoof" as the occasion arises. This may be a task of considerable magnitude without the help of the patient's physician.

MARK FALCON LESSES, M.D.
Chairman
Supervisory Committee on Blood Banks
of the Massachusetts Medical Society
MORTEN GROVE-RASMUSSEN, M.D.
Director, Blood Bank
Massachusetts General Hospital
Boston

BOOK REVIEW

The Neuroses in Clinical Practice. By Henry P. Laughlin, M.D. 8°, cloth, 802 pp., with 33 tables. Philadelphia: W. B. Saunders Company, 1956. $12.50.

Henry P. Laughlin, M.D., has had wide clinical experience in dealing with the neuroses not only in a civilian but also in a military capacity. At present he is consultant in psychiatry at the Walter Reed Army Medical Center, a post that gives him a unique opportunity to co-ordinate his views about neuroses as they occur in times of peace with similar reactions in a setting of combat.

This book represents prolonged and exhaustive research on his part with a vast quantity of material concerning the nonpsychotic disorders as they occur in men and women today. The introduction is reassuring, and the discussion of the nature of anxiety comprehensive. The concepts of emotional conflict are broad and illuminating. In presenting the problem of the anxiety reaction, the base is very broad, and the approach is eclectic. What the author has to say will be comprehensible to any educated person. Especially important is his emphasis on collaboration in therapy, which indicates his appreciation of the value of multiple therapy. Most interesting is the chapter on the mechanisms of defense that one develops inside his own personality; these mechanisms are described in a complete form with much elaboration. Two chapters present the phobic reactions in a way that is fresh and at the same time ageless. The author discusses in great detail the conditions of "secondary gain," which he calls, in his own words, "the illusory gains of emotional illness," and he describes very effectively the reactions of conversion, dissociation, depression and fatigue. He does not omit attention to abnormal preoccupations with physical health (or, as Schilder used to say, "distortion of the body image") and he devotes two chapters entirely to the obsessive-compulsive reactions. The last chapter deals with neuroses that follow trauma; this section alone runs to 113 pages.

This is not primarily a treatise on therapy, nor does it need to be. Basically, it is a well organized and very accurate descriptive volume about the clinical (and human) factors of neuroses considered *as neuroses.* Dr. Laughlin sets out to bring together everything he considers essential in this particular area, and he does it most conclusively. As I see it, no one has much reason to complain about the breadth and length of this book. One special interesting feature is that the author includes and weaves into the pattern appropriately many timely troubles. For example, the plight of Cardinal Mindzenty, "brain washing," electronics (which he introduces by means of an analogy related to repression) and Niagara Falls (which he relates to the concept of sublimation) and he does not forget Mesmer, Charcot, Janet, Breuer (the father of psychoanalysis) and Freud (who adopted and raised it).

Obviously, Dr. Laughlin has done an enormous amount of reading and research to bring together so much material in such a condensed form. If anything, the book suffers slightly from overorganization and overcondensation. It does not read as an essay, but it stands up remarkably well as a small encyclopedia and reference textbook.

MERRILL MOORE, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Excitability of the Heart. By Chandler McC. Brooks, Ph.D.; Brian F. Hoffman, M.D.; E. E. Suckling, M. Sc., M.E.E., Department of Physiology and Pharmacology, State University of New York College of Medicine at New York City; and Oscar Orias, M.D., Instituto de Investigacion Medica Mercedes y Martin Ferreyra, Cordoba, Argentina. With a foreword by Carl J. Wiggers, M.D. 8°, cloth, 373 pp., with 86 illustrations and 13 tables. New York: Grune and Stratton, 1955. $6.50.

Tumors of the Female Sex Organs: Hydatidiform mole and chorio-carcinoma. By Arthur T. Hertig, M.D., Shattuck Professor of Pathological Anatomy, Harvard Medical School, and consultant in pathology, Boston Lying-in Hospital and Free Hospital for Women, Brookline, Massachusetts; and Hazel Mansell, M.B.B.S., instructor in pathology, Harvard Medical School, and chief resident pathologist, Free Hospital for Women, Brookline. 4°, paper, 64 pp., with 65 illustrations, 6 tables and 2 colored plates. Washington, D.C.: Armed Forces Institute of Pathology, 1956. $1.00. (*Atlas of Tumor Pathology,* Section 9-Fascicle 33.)

Alcoholism as a Medical Problem: A Conference held under the auspices of the Committee on Public Health of the New York Academy of Medicine and the New York State Mental Health Commission. Edited by H. D. Kruse, M.D. 8°, cloth, 102 pp. New York: Paul B. Hoeber, Incorporated, 1956. $3.00.

A Manual of Practical Obstetrics. By the late O'Donel Browne, M.B., M.A.O., M.A., Litt.D., F.R.C.P.I., F.R.C.-O.G., master, Rotunda Hospital, Dublin, King's Professor of Midwifery, Dublin University, and gynecologist to the Stewart's Hospital, Co. Dublin. Edited and largely rewritten by J. G. Gallagher, M.D., M.A.O., F.R.C.P.I., M.R.C.O.G., assistant gynecologist, Mater Hospital, Dublin, consulting gynecologist, St. Michael's Hospital, Dun Laoghaire, visiting obstetrician, National Maternity Hospital, Dublin, and examiner in obstetrics and gynecology, University College, Dublin, and Royal College of Surgeons in Ireland. Third edition. 8°, cloth, 265 pp., with 203 illustrations. Bristol: John Wright and Sons Limited, 1956. $7.50. (Distributed in the United States by the Williams and Wilkins Company, Baltimore.)

A Follow-up Study of War Neuroses. By Norman Q. Brill, M.D., professor of psychiatry and superintendent and medical director, Neuropsychiatric Institute, University of California School of Medicine, Los Angeles; and Gilbert W. Beebe, Ph.D., statistician, Follow-up Agency, Division of Medical Sciences, National Research Council, Washington, D.C. 8°, cloth, 393 pp., with 11 illustrations and 271 tables. Washington, D.C.: Veterans Administration, 1956. (*VA Medical Monographs.*)

Das klinische Bild der Dauerfolgen nach Hirnverletzung. By Doz. Dr. med. Clemens Faust, Freiburg I.Br. 8°, paper, 91 pp., with 5 illustrations. Stuttgart: Georg Thieme, 1956. DM 7.80.- $1.85. (*Arbeit und Gesundheit,* No. 60.) (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

The Great Physiodynamic Therapies in Psychiatry: An historical reappraisal. Edited by Arthur M. Sackler, M.D., Mortimer D. Sackler, M.D., Raymond R. Sackler, M.D., and Felix Marti-Ibañez, M.D. 4°, cloth, with 2 illustrations and 2 tables. New York: Paul B. Hoeber, Incorporated, 1956. $5.75.

On the Early Development of Mind: Selected papers on psychoanalysis. Vol. 1. By Edward Glover, M.D. 8°, cloth, 483 pp. New York: International Universities Press, Incorporated, 1956. $7.50.

NOTICES

ARTHRITIS STUDY UNIT

The next two meetings for the Arthritis Study Unit will be held in the Fitkin Amphitheater, Yale–New Haven Medical Center, New Haven, Connecticut, on Thursdays at 3:30 p.m. The program is as follows:

November 15. The Diagnosis and Treatment of Gouty Arthritis. John H. Talbott, M.D.

January 17. Collagen Diseases. Joseph J. Bunim, M.D.

All interested physicians are invited to attend.

PHI DELTA EPSILON

A meeting of Phi Delta Epsilon will be held at the Fitkin Amphitheater, Yale–New Haven Medical Center, New Haven, Connecticut, Wednesday, November 28, at 8:15 p.m.

Dr. Gustaf Dammin will give a talk entitled "Tissue Transplantation — Current Studies on the Survival of Skin Homografts."

All interested physicians are invited to attend.

MIDDLESEX COUNTY SANATORIUM

The twenty-fifth anniversary celebration of the Middlesex County Sanatorium will feature a symposium on pulmonary disease. The symposium will be held at the Sanatorium, 775 Trapelo Road, Waltham, Massachusetts, Wednesday, November 28, at 2 p.m.

Dr. Kenneth Bird will act as moderator of a panel discussion on "Specific Drugs in Tuberculosis." There will be ten-minute presentations by staff members.

The speaker will be Dr. Merrill C. Sosman, who will give a talk entitled "Miliary Diseases of the Lungs."

NEW ENGLAND CARDIOVASCULAR SOCIETY

A meeting of the New England Cardiovascular Society will be presented by the Beth Israel Hospital and the Peter Bent Brigham Hospital in the Morse Auditorium, Museum of Science, Science Park, Boston, on Monday, November 5, at 8 p.m.

PROGRAM

Peter Bent Brigham Hospital, Samuel A. Levine, M.D., presiding:

Natural Life History of Constrictive Pericarditis: Treated and untreated. C. Sidney Burwell, M.D., Albert G. Bickelmann, M.D., Lloyd H. Ramsey, M.D., James B. Dealy, M.D., and Eugene D. Robin, M.D.

Catheterization of the Left Side of the Heart. Paul Novack, M.D., Robert Schlant, M.D., Arthur I. Phinney, Jr., M.D., Florence W. Haynes, Ph.D., and Lewis Dexter, M.D.

The Appraisal of "Rheumatic Activity" in Relation to Mitral-Valve Surgery. Joseph M. Miller, M.D., and Samuel A. Levine, M.D.

The Pulmonic Second Sound. John R. Blake, M.D., and Walter T. Goodale, M.D.

Beth Israel Hospital, Paul M. Zoll, M.D., presiding:

Some Clinical Implications of Experimental Pulmonary Embolism. Stanford Wessler, M.D., Jay H. Katz, M.D., and David G. Freiman, M.D.

Pharmacologic Studies in Experimental Complete Heart Block. Arthur J. Linenthal, M.D., Paul M. Zoll, M.D., Leona R. Norman, M.D., William Gibson, M.D., Hussein A. Shustari, M.D., Morris J. Seide, M.D., and Mrs. Beverly A. Fordyce.

Vectorcardiography in Pulmonary Embolism. Louis Wolff, M.D.

Free parking privileges are available on the premises at Science Park (emergency telephone number, RI 2-1410).

Interested physicians and medical students are cordially invited to attend.

SOCIETY MEETINGS AND CONFERENCES

OCTOBER 26. New York Academy of Medicine. Page 304, issue of August 9.

OCTOBER 26, 1956–APRIL 27, 1957. Postgraduate Medical Institute. Page 785, issue of October 18.

OCTOBER 29. University of Virginia. Page 627, issue of September 27.

OCTOBER 29 and 30. American Cancer Society. Page 785, issue of October 18.

OCTOBER 30 and 31. Consultation Clinics for Crippled Children in Massachusetts. Page 626, issue of September 27.

OCTOBER 30 and 31 and NOVEMBER 1. New England Postgraduate Assembly. Page 729, issue of October 11.

OCTOBER 31, NOVEMBER 14 and 28 and DECEMBER 12. Walter E. Fernald State School. Page 728, issue of October 11.

NOVEMBER 2. Massachusetts Society of Anesthesiologists. Page 785, issue of October 18.

NOVEMBER 4–8. American Institute of Dental Medicine. Page 675, issue of October 4.

NOVEMBER 5. New England Cardiovascular Society. Notice above.

NOVEMBER 7–9. American College of Obstetricians and Gynecologists. Page 731, issue of October 11.

NOVEMBER 12–16. American Public Health Association. Page 675, issue of October 4.

NOVEMBER 14–22. Pan-Pacific Surgical Association. Page 490, issue of September 6.

NOVEMBER 15, 1956, and JANUARY 17, 1957. Arthritis Study Unit. Notice above.

NOVEMBER 18–22. Pan American Medical Association. Page 490, issue of September 6.
NOVEMBER 28. Phi Delta Epsilon. Page 831.
NOVEMBER 28. Middlesex County Sanatorium. Page 831.
NOVEMBER 28–30. American College of Cardiology. Page 731, issue of October 11.
DECEMBER 14, 1956, and FEBRUARY and APRIL, 1957. Massachusetts Society for Research in Psychiatry. Page 56, issue of July 5.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, NOVEMBER 1

THURSDAY, NOVEMBER 1
New England Postgraduate Assembly. Hotel Statler, Boston.
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Dr. John Spellman and staff. Saint Elizabeth's Hospital.
8:00–9:00 a.m. Medical Journal Club. Joslin Auditorium, New England Deaconess Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Medical Grand Rounds. Dr. Sylvester McGinn and staff. Saint Elizabeth's Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m. Clinicopathological Conference. Dr. Benjamin Castleman and associates. Pathology Amphitheater, Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Surgical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*12:15–1:15 p.m. Tumor Clinic. Dr. T. W. Botsford. Amphitheater, Peter Bent Brigham Hospital.
*3:00 p.m. Thoracic Conference. The Natural History of Mitral Stenosis. Dr. Knud H. Oleson. Main Amphitheater, Peter Bent Brigham Hospital.

FRIDAY, NOVEMBER 2
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Members and Guests of the Joslin Clinic. Sulfonylurea Compounds. Dr. Raffael Camerini. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Medical Grand Rounds. Stearns Auditorium, New England Center Hospital.
*12:00 m. Pediatric Grand Rounds. Thorndike Amphitheater, Boston City Hospital.
*12:30–1:30 p.m. Surgical Grand Rounds. Stearns Auditorium, New England Center Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*2:00–3:00 p.m. Pathology Conference. Dr. James Graham. Saint Elizabeth's Hospital.
*4:00 p.m. Massachusetts Society of Anesthesiologists. Harvard Club, Boston.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.
*4:30 p.m. Neuroradiologic Conference. X-Ray Conference Room, New England Deaconess Hospital.

SATURDAY, NOVEMBER 3
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*8:30–10:00 a.m. Surgical Grand Rounds. Drs. Charles G. Child, III, A. J. A. Campbell and staff. First (Tufts) Surgical Service, New Cheever Amphitheater, Dowling Building, Boston City Hospital.
*9:00–10:00 a.m. Anesthesiology Conference. Dr. Benjamin Etsten. Anesthesia Laboratory, New England Center Hospital.
*9:30–11:00 a.m. Surgical House Officers' Conference. Second-Floor Conference Room, Carney Hospital, Dorchester.
*10:30 a.m. Teaching Ward Rounds. Ward South 2, Free Hospital for Women.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Hematology Conference. Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

MONDAY, NOVEMBER 5
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Staff Conference. Child Psychiatry. By appointment. Conference Room (Burnham 7), Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Pediatric Clinicopathological Conference. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*12:00 m.–1:00 p.m. Tumor Conference. Dr. C. C. Lund and members of the Tumor Board. Dowling Amphitheater, Boston City Hospital.
*12:00 m.–1:00 p.m. Metabolism Conference. Dr. Schwartz. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. X-Ray Conference. Dr. William Carey. Saint Elizabeth's Hospital.
*3:00–4:00 p.m. Neuroradiologic Conference. Dr. Bertram Selverstone. Stearns Auditorium, New England Center Hospital.
*4:00 p.m. Clinicopathological Conference. Pathology Conference Room, Beth Israel Hospital.
*4:00–5:30 p.m. Anesthesiology Conference. Avertin and Rectal Anesthesia. Dr. E. J. Wolley. Surgical Conference Room, Peter Bent Brigham Hospital.
*4:00–5:30 p.m. Anesthesiology Conference. Dr. Benjamin Etsten. Stearns Auditorium, New England Center Hospital.
*5:00–6:30 p.m. Anesthesia Group of the Lahey Clinic. Joslin Auditorium, New England Deaconess Hospital.
*7:00–9:00 p.m. Slide Seminar in Pathology. Dr. Edward T. MacMahon. Stearns Auditorium, New England Center Hospital.
*7:00–9:00 p.m. Anesthesia Teaching Conference of Greater Boston. Panel Discussion. Comparison of Spinal Anesthesia Technics. Dr. Zentgraf. Auditorium, Jimmy Fund Building, Children's Medical Center, 35 Binney Street.

TUESDAY, NOVEMBER 6
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical Grand Rounds. Pathology Conference Room, Carney Hospital, Dorchester.
*10:30 a.m. Medical Grand Rounds. Main Conference Room (Grounds 1), Lemuel Shattuck Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m.–1:00 p.m. Pediatric Grand Rounds. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Gastrointestinal or Allergy Conference. Dr. Stanley or Dr. McCombs. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Hematology Conference. Dr. Mario Stefanini. Saint Elizabeth's Hospital.
*5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Service Meeting Followed by Clinical Conference (Medical, Surgical, Obstetric). Faulkner Hospital.

WEDNESDAY, NOVEMBER 7
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. Dr. Grounds 1st. New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Auditorium, Carney Hospital, Dorchester.
*9:00–10:00 a.m. Surgical Grand Rounds. Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Orthopedic Grand Rounds. Bigelow Amphitheater, White 3A, Massachusetts General Hospital.
*11:00 a.m.–12:00 m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:00 m.–1:00 p.m. Boston State Hospital Psychiatry Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Roentgen Diagnostic Conference. 5th-floor teaching unit, Beth Israel Hospital.
*12:00 m.–1:00 p.m. Neurology, Neurosurgery and Psychiatry Conference. Drs. John F. Sullivan, Justin Hope and Bertram Selverstone. Stearns Auditorium, New England Center Hospital.
*12:00 m.–1:00 p.m. Pediatric Medical-Surgical Rounds. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*12:00 m.–1:00 p.m. Pediatric Clinicopathological Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:15 p.m. Vascular Rounds. Drs. Edward A. Edwards and Chilton Crane. D-Main, Peter Bent Brigham Hospital.
*12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. The Clinics of the Massachusetts General Hospital.
*2:00 p.m. Rectal Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*6:30 p.m. Lahey Clinic Lecture. Fluid and Electrolyte Balance. Dr. George O. Bell. Joslin Auditorium, New England Deaconess Hospital.

*Open to the medical profession.